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by M. A. Aliyev and R. I. Kulakova

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ANNOTATION

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This monograph illuminates problems in the development and course of experimental atherosclerosis against a background of renovascular hypertonia and their interaction in long-term acclimatization with consideration of the meteorological and heliogeophysical factors operating in the high mountains. Incidental data on the variations of cholesterol, lecithin, and the lecithin-cholesterol coefficient under the conditions of low and high mountains are presented as they depend on season. The monograph is oriented to physicians and scientific workers.

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Chapter I

HYPERTONIA AND ATHEROSCLEROSIS /3

Incidence of hypertonia under lowland and alpine conditions. A substantial body of literature data indicates that arterial pressure is adjusted to lower levels at certain localities on the earth.

Donnison (1929) investigated the blood pressure of 1,000 African Negroes and did not observe a single case of high arterial pressure.

In Egypt, according to Elam and Smerk (A.L. Myasnikov, 1960), blood pressure is 10-30 mm Hg lower than in Europe and America. In only a few cases was the pressure level between 140 and 150 mm Hg; in the opinion of the authors, this should be regarded as extremely high for Egyptians.

Gauston (1965) reports that during four years of work in China he did not encounter a single patient with high blood pressure; there, hypertonia is associated only with nephritis. According to his data, Chinese have blood pressures 20 mm Hg below those of Americans. The blood pressure of Americans who went to China decreased.

The domestic literature contains a considerable amount of material on the incidence of hypertonia in the Soviet Union. Tabulation of the results of mass physical examinations in the USSR indicates that the average arterial-pressure level and the frequency of hypertonia depend on local climatic and geographic conditions.

The climate of the North tends to lower arterial pressure. M.S. Turkel'taub (1949) reported a tendency to lower blood pressure in a mass study of the inhabitants of Arkhangel'sk. A.G. Paranskiy (1949) also observed predominance of the hypotonic state above the Arctic Circle: systolic pressure was below 100 mm Hg in 19.2% of individuals and above 140 mm Hg in 1.8%. The diastolic pressure was below 60 mm Hg in 18.5% of those examined, /4
and above 900 mm in 1.5%.

Of 600 residents of the Moscow area examined by I.M. Kurmanovskaya, S.N. Chernyakov, Ye.A. Ivanov, and I.R. Yemel'yanova (1952), 5-6% were afflicted with hypertonia.

In routine examinations of workers and staff of industrial enterprises in the same Moscow area in 1952, L.P. Presman, Ts.Ya. Kogan, and L.L. Atlasova (1952) established that of 434,397 persons, about 6.4% exhibited true hypertonia, while 7.6% were found to be prehypertonic.

A.B. Shakhnazarov (1953) reported a lower (4%) incidence of hypertonia under the conditions of the moderately warm climate of the Southern Crimean coast as compared with the steppes farther to the north in the Crimea (7%), which are characterized by frequent and sudden temperature and wind-force changes, especially during the autumn and winter months.

In a study of Astrakhan boatmen, Ye.I. Abol'yanina (1954) found hypertonia in 118 (6.1%) of 1910 persons.

Working from blood-pressure measurements made on the population of Baku, D.M. Abdullayev (1955) established the presence of the hypertonic state in 5.4% of the 10,000 subjects examined.

In the republics of Central Asia with their hot climates, a tendency for the normal arterial-pressure level to decrease by about 10 mm Hg (both systolic and diastolic) and a lower incidence of hypertonia as compared with the middle belt of our country have been reported. This is especially striking during the hot months of the year (P.A. Chernysh, 1951; V.M. Avakyan, 1959; D.M. Allaberdyyev, 1961; Z.I. Umidova et al., 1961; Kh. Kh. Mansurov and Z.A. Kostenko, 1961).

It will be seen from the above data, which pertain for the most part to the European part of the Union, that the incidence of hypertonia is different in different regions.

Many Soviet and foreign specialists have studied arterial pressure and pulse rate under alpine conditions, but for the most part in healthy persons.

Statements regarding a presumably unfavorable effect of the mountain climate on hypertonic patients with signs of cardiovascular insufficiency are found in the literature.

Ts.A. Levina (1949) examined persons who had vacationed at the mountain health resort (1480 meters) at Chimgan in Uzbekistan and reported a favorable effect of the mountain climate on patients with heart trouble, myodystrophy, and signs of first- /5
degree cardiovascular insufficiency. Their blood pressures were also lowered.

A.P. Zhukov (1949) examined lifelong residents of Western Pamir (2500 meters) and persons who had moved there from lower elevations with pronounced signs of hypertonia. As a rule, their systolic and diastolic arterial pressures were lower at the 2500-meter elevation. At the time, the author recommended that residence at such moderate elevations be tested as a means of treating certain forms of arterial hypertonia. According to the same author, systolic pressure was again higher at a higher elevation (about 4000 m) in the Eastern Pamir, even in young persons around 20 years of age, but decreased somewhat even after a two-week stay. The author concludes that elevations above 300-3500 m are contraindicated for persons with manifest and latent forms of hypertonia.

N.P. Afonskiy (1953) also recommended treatment of hypertonics under the conditions of the alpine health resort at Isti-Su (2200 m).

M.E. Yefendiyev, S.M. Bedalova (1958) and D.K. Akhundov (1959) observed a lowering of arterial pressure in 10 hypertonics ranging in age from 39 to 74 years under the medium-elevation conditions of Shushi (1304 meters).

G.M. Gukasyan (1963) reports a normalization of pressure in first- and second-stage hypertonia patients after a stay at the Mrovdag mountain health resort.

N.N. Sirotinin (1963), who was predisposed to hypertonia himself, reported a favorable effect of the high-mountain climate in vascular dystonias (his arterial pressure would rise to 170 mm Hg and above, but would decrease with each ascent of Mt. El'brus).

It would be interesting to determine the incidence of hypertonia as a function of the local elevation. G.I. Mataishvili (1965) examined herdsmen living at elevations of 2000-2500 m, vintners at 750-800 m, and tobacco workers at 250-350 m. Sex and age were taken into account in this study. It was found that hypertonia is twice as frequent among persons living at elevations of 250-350 m as in those living in the high mountains.

P.N. Kipshidze, N.T. Chumburidze, G.E. Chapidze, N.I. Katamadze, A.L. Samadalashvili, and N.V. Samoylova (1965) made a full-coverage study of the incidence of hypertonia as a function of /6
sex, age, and occupation in the high mountains of Georgia (1200-1250 meters).

Hypertonia was observed in 13.9% of cases, occurring most frequently in persons whose work involved nervous strain and those who abused alcohol.

Both clinicians and experimentors have recently become interested in questions as to the effect of the high mountains of Kirgiziya on the course of hypertonia.

M.A. Aliyev and V.A. Volkova (1959) studied the incidence of hypertonia among employed residents of Przhevalsk (1750-1800 m). They established hypertonia in 4% of 2509 subjects. This figure is substantially lower than those for lowland towns.

In 1959-1964, M.A. Aliyev studied the influence of the high mountains of Kirgiziya on the course and development of renovascular hypertonia. The results of his experimental investigations indicated that the climate of the middle- and high-elevation localities (1800, 2150, 1700, 3200 m) has an inhibiting effect on the development of hypertonia due to functional disturbance of one of the neurohumoral blood-pressure regulatory links of the reninangiotensin-aldosterone system. When both kidneys are involved in the pathogenetic chain (bilateral constriction), the high-mountain climate is less effective in inhibiting the development of hypertonia.

L.G. Filatova (1961) examined persons living at comparatively low elevations in the mountains (from 760 to 2400 meters above sea level) and found that hypertonics were rare among them. The author reports that a journey into the mountainous area of the Tien-Shan was often accompanied by a lowering of arterial pressure.

Z.S. Moiseyeva (1963) reported a decrease in arterial pressure in dogs with pituitrin hypertonia at an elevation of 3200 m.

In animal experiments, M.A. Aliyev and S.I. Arestova (1964) reported inhibition of the desoxycorticosterone and renal-desoxycorticosterone forms of experimental hypertonia under high-mountain conditions.

M.A. Aliyev (1964) writes: "The nature of the weather and heliogeophysical factors operating in the high mountains is also an important factor in pressor-depressor arterial-pressure displacements in this severe form of hypertonia: a favorable combination of these conditions (moderate temperature and low air humidity, relatively constant barometric pressure, intense solar /7
and ultraviolet radiation, negative aeroionization, windless and rainless days, etc.) does not produce meteorotropic disturbances. However, a negative complex of meteorological factors in the mountains (low air temperature and high air humidity, falling barometric pressure, sunless days, torrential rains, early snows, strong winds, electrical disturbances, etc.) tend to promote pressor displacements in hypertonia."

Variations in lipid content in hypertonia and atherosclerosis under lowland and high-mountain conditions. On observing hypercholesteremia in 75% of his patients, Westphal (1924), one of the first to investigate lipids in hypertonia, advanced the hypothesis that an excess of cholesterol in the blood has a sensitizing effect in which arterial tonus is consistently elevated. On this basis, he raised the question as to whether the development of hypertonia depends on blood cholesterol level. However, subsequent studies by A.L. Myasnikov (1924), I.G. Gel'man (1927), Ye.M. Tareyev and N.A. Ratner (1938), N.D. Strazhesko (1940), Ye. I. Tsukershteyn and M.N. Yegorova (1949), G.F. Lang (1950), K.V. Shagalova and P.L. Estrina (1952), Fischberg (1954), S. Kochekmadze (1955), and Waris (1958) failed to establish any relation between cholesterol level and blood pressure.

While noting a tendency to hypercholesteremia in certain hypertonics, G.F. Lang (1950) at the same time negated any possible effect of the elevated cholesterol level in the blood in regard to aggravation of the angiospastic phenomena. Fischberg (1954) considers that neither hypercholesteremia nor hyperlipidemia can by itself cause a rise in arterial pressure.

However, certain authors have reported correspondence between a rise in blood cholesterol and persistently high blood pressure.

According to Harris et al. (1949), the level of hypercholesteremia is directly proportional to systolic blood pressure. Most authors have attributed the increasing hypercholesteremia in hypertonia to the atherosclerotic process (A.L. Myasnikov, 1924; A.I. Gruzin, 1952; Ya.N. Rozhdestvenskiy, 1951; B.V. Il'inskiy, 1940, 1954, 1960).

According to E. Kalnyn' (1954), the rise in cholesterol level regularly begins at the functional stage of hypertonia, and cholesterol content increases more significantly only with transition to the sclerotic stage. A few cases of hypercholesteremia are reported in other papers devoted to this problem. /8

A.L. Myasnikov and D.M. Grotel' (1926), V.M. Kogan-Yasnyy (1940), L.A. Brodovich (1946), B.V. Il'inskiy (1954), and G.Z. Ishmukhametova (1957) found hypercholesteremia in 50-63% of hypertonics; according to M.O. Levinson (1940), F.I. Litvak and I.M. Sosnina (1954), and S. Kochekmadze (1955), it was observed in 29-46% of cases, but L.I. Yegorova (1950) notes high blood cholesterol in only 25% of her patients.

Some authors are inclined to reject any increase in cholesterol level in hypertonia. Page, Kirk, and Van Slyke (1936) and Elliot and Nuzum (1936) found hypercholesteremia in only occasional cases of hypertonia.

G.V. Drobova (1948) observed the most striking blood-cholesterol rise in the renal form of hypertonia, and linked it to the kidney damage.

According to Volhard and Fahrt (1914), Keith, Wagener, and Kernohan (1928), Ellis (1938), and Ye.M. Tareyev (1948, 1952), a pernicious and rapidly progressive course of hypertonia is characterized by persistently elevated arterial pressure, especially diastolic, severe visual disturbances, etc. In such cases, it is closely simulated by experimental renal hypertonia.

The phospholipid-cholesterol ratio is given a great deal of attention in study of lipid metabolism in atherosclerosis. In the opinion of Peters and Man (1943), Morrison (1952), and Yu.T. Pushkar' (1953), a decrease in this ratio is an atherogenic factor and, according to Kellner (1952), is a more reliable reflection of the atherosclerotic process than the blood cholesterol level.

The pathogenetic significance of a decrease in this coefficient was established by the studies of Boyd (1937), Ahrens and Kunkel (1949), S.V. Nedzvetskiy and S.S. Ratnitskaya (1951) and others, who found that phospholipids have a stabilizing effect on the colloidal state of cholesterol in the blood.

The hydrophilic properties of the phospholipids, which are capable of forming stable emulsion systems, form the basis for this effect. Adsorbed on particles of cholesterol, phospholipids render its solution in the blood plasma stable and, as it were, protect it from precipitation and deposition. A blood phospholipid content that is deficient with respect to the amount of /9
cholesterol results in a weaker stabilizing action of the phospholipids.

A tendency to lower phospholipid-cholesterol ratios in hypertonia was reported by Ya.N. Rozhdestvenskiy (1952), Katz and Stamler (1953), and B.V. Il'inskiy (1954, 1960), who attributed this decrease to a disproportionately high cholesterol content as compared with the normal or near-normal phospholipid level. B.V. Il'inskiy found that the most pronounced and stable decrease in this coefficient occurred against a background of significant atherosclerotic changes.

Other investigators – N.D. Strazhesko (1940), A.M. Fischberg (1954), and S.Kochekmadze (1955) – report an increase in all lipid fractions (including phospholipids) in hypertonia.

Thus, S. Kochekmadze found an increased lipid-phosphorus concentration in the blood serum of 54% of his hypertonic patients and hypercholesteremia in only 46%, so that an increase in the phospholipid-cholesterol coefficient was observed in 28%.

We have found little information in the literature on the influence of the high mountains and oxygen insufficiency on lipid metabolism in hypertonics. Kh.I. Vaynshteyn (1948) reports hypercholesteremia in cases of cardiac decompensation, pernicious anemia, inflammation of the lungs, hypertonia and atherosclerosis, i.e., in states that may be characterized by oxygen starvation of varying degree and origin.

In the high mountains of Kirgiziya (1750 m), A.Ya. Shurygin (1962) reported disturbance of adipolipid metabolism in second- and third-stage hypertonia patients: a tendency to hypercholesteremia, lowered lecithin content, and a lower lecithin-cholesterol ratio.

Atherosclerosis, the grave and common disorder that affects vitally important segments of the human cardiovascular system, chiefly the arteries of the heart and brain — was for a long time not distinguished from the general class of arteriosclerotic disorders of miscellaneous origin. Its causes were sought in thickening of the intimae of vessels due to deposition of coagulated proteins, inflammation of the vascular wall, and a subsequent reactive thickening of the wall. Some investigators placed emphasis on mechanical, infectious, and toxic causative factors (Z.F. Orlovskiy, 1905, I.G. Kalamkarov, 1907).

Ribbert (1904) attached great importance to the blood pressure: plasma, impregnating the inner lining of the arterial wall, compresses it, and this is followed by fatty enlargement of the cells of the intima. /10

Ashof (1935) demonstrated that the atheroma consists principally of cholesterol esters, which are initially found not in the cells of the intima, but in the intercellular substance.

It was not until experimental work was done by Soviet scientists that the first light was shed on the pathogenesis of atherosclerosis.

By forced feeding of rabbits with various types of animal food (bouillon, milk, chicken eggs) A.I. Ignatovskiy and S.N. Saltykov (1907-1908) succeeded in producing changes in the aorta that resembled those observed in the initial stage of atherosclerosis in man.

In the classical experiments on which the modern infiltration-hypoplastic theory of the pathogenesis of atherosclerosis was based, N.N. Anichkov (1912) showed that the addition of cholesterol to the diet of rabbits results in their developing pronounced vascular changes similar in morphology to atherosclerotic vascular damage in the human.

In addition to the disturbances to metabolic processes, which apparently play a major role in the pathogenesis of atherosclerosis, there are factors that objectively promote its development. This is well illustrated by the presently accepted theory of Academician N.N. Anichkov, who writes: "Factors of importance in the etiology of atherosclerosis include, firstly, general factors in the form of disturbances to cholesterol metabolism associated with the accumulation of large amounts of this substance in the organism and, secondly, factors of local nature, which create especially favorable conditions in the arterial walls for the deposition of cholesterol. It is the combination of the general causative factor with the local predisposition that results in the development of atherosclerosis" (1925, page 216).

L.M. Starokadomskiy (1909), N.V. Stukkey (1910), N.V. Veselkin (1912), S.S. Khalatov (1917), N.N. Anichkov (1912-1913), and D.D. Krylov (1916) reproduced genuine atheromatous lesions in rabbits, some even with calcium deposits, and found that chicken-egg yolks were the most potent experimental causative factor (N.V. Stukkey, 1910).

The hypothesis was advanced (N.V. Veselkin, S.S. Khalatov, N.N. Anichkov) that the active part of eggyolk, that which triggers the development of the experimental atherosclerosis, is cholesterol. According to the metabolic theory of atherosclerosis, cholesterol is of prime importance in the development of the disease. "All investigators have reported," wrote N.N. Anichkov (1953), "that the principal source of the cholesterol deposit in atherosclerosis is exogenously introduced cholesterol. This has been established beyond a doubt in regard to experimental cholesterol atherosclerosis." /11

It has been proven experimentally that the subsequent conversions of exogenously ingested alimentary cholesterol are complex and depend on the factors that regulate lipid metabolism. Observations have shown that populations whose diet includes large amounts of animal fats have blood cholesterol contents at a higher level than that in populations whose diet is largely vegetarian (A.L. Myasnikov, 1961; I.S. Glazunov, 1961; Keys, Fidanze, and Scardi, 1952, and others).

True, the question as to the causes of the differences in blood-cholesterol level between different peoples has not yet been finally answered, and it cannot be on the basis of data on alimentary factors in cholesteremia alone. Many authors also take account of hereditary, social, geographic, and other factors. However, the effects of diet have been convincingly demonstrated. To a certain degree, the unequal blood-cholesterol levels in the populations of various countries correspond to different rates of atherosclerotic disease.

Atherosclerosis is a disease related to disturbance of lipid metabolism.

The great importance of cholesterol in the development of atherosclerosis has been confirmed by the results of many investigators who have reported elevated cholesterol in the blood of most atherosclerosis patients. Back in 1924, A.L. Myasnikov established an abnormally high cholesterol level in the blood of 30-70% of atherosclerosis patients. On the basis of a careful clinical analysis of the results, the author arrived at the conclusion that hypercholesteremia occurs in patients with pronounced manifestations of atherosclerosis and is characteristic for the progressive course of the disease.

A.P. Yakovleva and L.S. Shvarts (1929) observed a prolonged (48-hour) rise in the blood cholesterol levels of atherosclerosis, nephrosis, and nephritis patients with nephrolytic component after a single administration of 2 grams of the substance.

Gertler and Garn (1950) also reported that hypercholesteremia often occurs in combination with atherosclerosis.

B.V. Il'inskiy (1951) suggests that an increase in blood /12 cholesterol, especially over the long term, may indicate a danger of atherosclerosis even in healthy persons. Buck and Rossister (1951) express a similar view as to the diagnostic significance of hypercholesteremia in atherosclerosis.

There are indications that cholesterol exchange is regulated in the organism in such a way that the synthesis of endogenous cholesterol is inhibited in response to alimentary hypercholesteremia (M.G. Kritsman, M.V. Bavina, 1956); at the same time, cholesterol can be synthesized not only from fats, but also from carbohydrates and proteins. However, there are cases in which clinically manifest atherosclerosis is not accompanied by a rise in the blood cholesterol level. Thus, in the observations of A.L. Myasnikov (1924), N.A. Sokolov (1925), and B.V. Il'inskiy (1938), hypercholesteremia was by no means always attended by atherosclerosis. On the other hand, the presence of hypercholesteremia does not necessarily result in the development of atherosclerosis (A.L. Myasnikov, 1927).

As a rule, experimental atherosclerosis can be produced quickly in animals in which manifest hypercholesteremia can be induced on a more or less prolonged basis (rabbits, guinea pigs). Here the degree of atherosclerosis is higher the higher the cholesterol level, although the correspondence between them is not perfect. Typical atherosclerotic changes were obtained even in the absence of noticeable hypercholesteremia only after prolonged (more than two years in N.N. Anichkov's experiments (1925)) feeding of small cholesterol doses to rabbits. It is nevertheless impossible in most cases to produce experimental atherosclerosis in animals without a stable, long-term elevation of blood cholesterol. But it is not possible to produce atherosclerotic changes in some carnivorous and omnivorous animals (rats, dogs, foxes), whose diets contains fats as a constant ingredient, by feeding them cholesterol. These animals have a better-developed lipid-metabolism-regulating apparatus, and it is not possible to produce stable hypercholesteremia in them by alimentary means. Thus, it is not sufficient merely to add cholesterol to the food to disturb the lipid metabolism of the dog; it is also necessary to use methylthiouracyl to suppress the function of the thyroid gland, one of the entities that regulate lipid metabolism.

Not only the amount of cholesterol, but also the state in /13 which it is present in the blood are essential factors in the development of atherosclerosis. As long ago as 1915, N.N. Anichkov pointed to the importance of the physicochemical state of the cholesterol in the pathogenesis of atherosclerosis. Later (1937), he stressed that the stability of the cholesterol suspension depends on the proportions of the individual lipids. It is regarded as proven that retention of cholesterol in the plasma (a hydrophobic colloid) in the dissolved state is promoted by phospholipids (hydrophilic colloids).

Various phosphorus-containing lipids compose the phospholipids: lecithin, cephalin, sphingomyelin, etc. Lecithin constitutes about 90% of the phospholipids and therefore participates more than the others in the organism's metabolic processes. The liver, the adrenal medulla, and nerve tissue are rich in phospholipids (G.M. Shershevskiy, 1936).

We know that lipids form a colloidal suspension in water. Blood serum contains large amounts of lipids, but is nevertheless usually transparent. Whether it is transparent or turbid depends on the quantity of colloidal lipid particles suspended in it. A decrease in the content of phospholipids results in precipitation of cholesterol from solution into a deposit.

A quite distinct inhibition of atherosclerosis can be obtained under experimental conditions by artificially raising the blood phospholipid level.

The inhibiting action of phospholipids on the development of atherosclerosis has been demonstrated by many investigators. Study of the epidemiology of atherosclerosis has shown that atherosclerosis is less frequently encountered in populations with high blood phospholipid contents. Thus, Schwartz (1957), Dewey (1916), Peters (1953), and Smith (1957) have drawn attention to the higher phospholipid level (together with a comparatively low cholesterol level) among Australians. Natives suffer from atherosclerosis relatively rarely. The phospholipid content of the blood depends on various exogenous factors, which usually change the phospholipid level in the same direction as the cholesterol level. Hypercholesteremia is usually accompanied by an increase in phospholipid level. For example, an increase in the blood lecithin level is also observed after a cholesterol meal. Single but long-term fat loads cause a stable increase in the levels of both cholesterol and phospholipids in the blood.

A disturbance of the equilibrium among the lipids occurs in atherosclerosis. In the view of many authors (M.G. Kritsman and M.V. Bavina, 1952; Taylor and Gould, 1950), quantitative changes in the phospholipids follow larger variations of the blood cholesterol content, but since their variations are not as strong, the proportioning of the lipids is disturbed. /14

The increase in the amount of phospholipids tends to hold the cholesterol in solution, and is regarded by some investigators as a protective reaction of the organism to the cholesterol increase (Leytes, 1937; B.V. Il'inskiy, 1954; G.M. Shershevskiy, 1956). Zilversmit, Shore, and Ackerman (1954) established that only one-tenth of the phospholipids in the aorta is of hematic origin, while the remainder are synthesized in the vessel wall itself. In atherosclerosis, phospholipid synthesis takes place at five times the normal rate. These authors also regard the accelerated synthesis of phospholipids in the aorta as a protective reaction of the organism to the increased amounts of cholesterol in the blood and in the vascular wall. As a result of this reaction, the cholesterol in the intimae is dissolved and enters the lumina of the vessels, i.e., the lipid plaque is resorbed.

The absolute cholesterol level is only partially characteristic of the state of lipid metabolism. It is also nesessary to consider the phospholipid-cholesterol ratio. A low lecithin-cholesterol coefficient indicates predominance of cholesterol over the phospholipids and the possibility that it may be deposited.

The pathogenic significance of the phospholipids and, in particular, of the cholesterol-phospholipid ratio in atherosclerosis have been established in the clinic. Peters and Van Slyke (1946) compared the cholesterol-phospholipid ratios in healthy and atherosclerotic individuals. In some cases, this index was also high in healthy persons with the same blood-cholesterol levels as the patients, but the latter had much higher cholesterol-phospholipid ratios.

Gertler and Garn (1950) found a high cholesterol-phospholipid ratio not only in atherosclerosis, but also in disorders that predispose to it (diabetes, nephrosis, etc.).

B.V. Il'inskiy (1940), Gertler, Garn, and Lerman (1950), Ya. N. Rozhdestvenskiy (1952), S.L. Gol'tskener (1954) A.A. Kleopina (1956) and others have drawn attention to the lower lecithin-cholesterol ratios of atherosclerosis patients.

M.V. Bavina (1951) and Yu.T. Pushkar' (1953) have established experimentally the presence of a definite relation between the lecithin-cholesterol coefficient and the degree of lipid accumulation in the aorta: the lower this ratio, the more pronounced the lipidosis of the aorta. /15

Kellner, Correl, and Ladd (1949, 1951) also reported that an increase in the blood lecithin level inhibits the development of experimental atherosclerosis. The latter was less pronounced in rabbits given lecithin simultaneously with a high-cholesterol diet.

All of the above indicates that phospholipids are an important factor in cholesterol stabilization and thereby prevent the development of atherosclerosis in animals and man.

Much study has been given to lipid metabolism in oxygen deficiency. Fenn (1940) and others have found that lipemia occurs in anoxia incurred at high elevations. They offered no precise explanation for this phenomenon. Maclachman (1939) noted only that the considerable fluctuations of the blood cholesterol of various animals under oxygen starvation are apparently to be explained by different reactions to it and different abilities of different animals to utilize fats.

According to Schemensky (1937), the normal cholesterol content under low-mountain conditions varied from 180 to 200 mg-%, while at Davos (elevation 5100 feet), the local inhabitants showed cholesterol levels ranging up to 350-480 mg-%. The cause of the increase remained unclear to the author.

British scientists (Altland, 1960) studied the influence of pressure-chamber "altitude" (4900 m) on cholesterol content in rabbits. After 17 days at "altitude," animals that received the usual diet showed no changes in blood-serum cholesterol concentration, but this concentration rose in animals to whose food cholesterol was added.

Oxygen has the opposite effect on lipid metabolism and the development of the atherosclerotic process. I.V. Maksimova (1958) showed that the blood cholesterol levels of atherosclerotic patients dropped significantly after long-term breathing of high oxygen concentrations.

Observations of the cholesterol-content changes in atherosclerosis and hypertonia patients who breathed oxygen in oxygen tents were made on a large scale in the clinic by V.A. Lisovskiy /16
and G.N. Khlybov (1958), who reported that the cholesterol level in the blood of most of the patients studied dropped substantially as a result of a single oxygen treatment (for 3-4 hours at an oxygen concentration of 50-60% under the tent).

Altschul and German (1954) and Altschul (1955) observed that the administration of cholesterol to animals kept in chambers in which the oxygen concentration was elevated (to 60-65%) sharply inhibits the development of experimental atherosclerosis. In their opinion, the effectiveness of the oxygen therapy depends on the length of the treatments: in animals that stayed in the chamber for extended periods, atherosclerosis was found to be less pronounced or totally absent. Similar experiments by V.A. Lisovskiy and G.N. Khlybov (1958) also showed that inspiration of elevated oxygen concentrations by animals slows down the development of experimental atherosclerosis.

Reciprocal relation between hypertonia and atherosclerosis. The frequency of cases in which hypertonia and atherosclerosis occur together was noted long ago. Over many years, there were frequent changes in opinion as to the relation between these illnesses. At the middle of the last century, hypertonia was regarded as a direct consequence of atherosclerosis. But even Juschar (1889) reported cases of hypertonia that were, in his words, without morphologically demonstrable atherosclerosis. Bergman proposed the term "hypertonia" during the 1920's. Finally, in 1922, V.F. Lang gave a clear-cut definition of hypertonia as a nosological entity with characteristic pathogenesis and its own clinical manifestations. Atherosclerosis came under study along with hypertonia as a specific disease of the cardiovascular system.

The pathogenetic reciprocal relationships between atherosclerosis and hypertonia are complex. A.L. Myasnikov (1959) showed that the two processes can influence one another in either direction – stimulation or inhibition.

The literature offers three viewpoints on this question. According to one of them, hypertonia inhibits the development of atherosclerosis. P.P. Dvizhkov (1948) affirms that atherosclerosis is more frequently encountered not among hypertonics, but among persons with normal and low blood pressure; in his opinion, hypertonia inhibits the development of atherosclerosis. As proof, he cites the fact that the pernicious course of atherosclerosis is not as strongly in evidence in hypertonia. However, neither this opinion nor the supporting arguments for it are shared by other authors, since the atherosclerotic process does not appear /17 to have time to develop during the progressive course of hypertonia with early lethal outcome.

A number of investigators have concluded that hypertonia has no influence on the developement of atherosclerosis. N.I. Konoval'chik (1940) compared the incidence of atherosclerotic changes in the aorta and in the coronary vessels in hypertonia on the one hand with normal blood pressure on the other and concluded that manifest atherosclerosis is encountered equally frequently in individuals with high and normal pressure. She stated that angina pectoris is encountered no more often in hypertonia than when blood pressure is normal.

V.G. Popov (1960) studied 779 case histories of myocardial infarct (529 with high and 250 with normal arterial pressure) and concluded that the course of atherosclerosis is equally grave both with hypertonia and at normal pressure. On this basis, the author infers that atherosclerosis is not a complication of hypertonia, but an independent process, and that these diseases often develop concurrently.

According to V.G. Popov and L.D. Grinshpun (1951), 54.8% of 177 myocardial infarct fatalities had had normal arterial pressure and 45.2% hypertonia, i.e., normotonics are encountered more frequently among those who have sustained infarcts. These authors suggest that elevated arterial pressure does not have a stimulating effect on the course of coronary atherosclerosis.

The literature also contains numerous references to atherosclerotic vascular damage in kidney patients, including those with the nephrotic syndrome. In particular, it is noted that in cases of kidney damage, even those with high cholesteremia, atherosclerotic damage to the vessels is rare. Thus, Aleksandrova (1945) found no atherosclerotic damage to the vessels in 97 out of 100 autopsied cases of the lipidonephritic syndrome. Marked hypercholesteremia had been observed in these patients during life.

N.A. Ratner and G.L. Spivak (1960) observed atherosclerosis in 6% of cases of chronic nephritis with hypertonia and manifest cholesteremia, but in 39% of hypertonia patients. According to autopsy data published by V.A. Vlasova (1960), atherosclerosis is encountered in 21.4% of cases as a complicating companion illness /18
with kidney diseases.

Among six autopsied cases of chronic glomerulonephritis of the hypertonic form, A.A. Zhukova (1963) noted vascular damage only in three, and even in these cases it was minor. In all of these cases, there had been a high degree of hypertonia, and three of the patients showed high cholesterol levels. Obviously (according to A.L. Myasnikov), some factors that mitigate the atherosclerotic process must come into play in cases of hypertonic damage to the kidneys.

It is generally accepted that hypertonia contributes to a more rapid and severe development of atherosclerosis. On this subject, A.L. Myasnikov writes: "Experimental as well as clinical-anatomical observations indicate that the attack on hypertonia is among the preventive measures against atherosclerosis" (1953, page 13).

Sydenstricker (1933) believed that there is a direct relation between blood-pressure level and the degree of atherosclerotic manifestation. Wakerlin (1952) also concluded (from autopsy data) that "chronic arterial" hypertonia favors the development of atherosclerosis, since 60% of patients with stable high blood pressures already showed signs of atherosclerosis at the time of diagnosis of the latter. Rau (1956) found severe atherosclerosis in 30-40% of hypertonic patients, while the figure was 5-10% among persons with normal blood pressure.

In an autopsy study of the hearts of hypertonics, Glawson and Bell (1941) recorded severe coronary sclerosis in 45% of cases, moderate sclerosis in another 45%, and insignificant sclerotic changes in the coronary arteries in only 10% of cases.

The work of V.D. Tsinzerling (1926), K.G. Volkova (1946), A.V. Smolyanikova and T.A. Naddachina (1961) indicates that the vessels subject to the strongest mechanical action of the bloodstream are most susceptible to atherosclerotic damage. In the opinion of N.N. Anichkov and V.D. Tsinzerling (1953), the aggravating effect of hypertonia on the development of atherosclerosis is due to an increase in vascular permeability when the arteries remain in the spastic state for long periods and to trophic changes that arise in them. Deviations in the physical properties of the vascular wall, and especially of its elastic elements, are a major factor here. By itself, a rise in arterial pressure does not /19 cause atherosclerotic changes; it is merely a secondary factor in the pathogenesis of atherosclerosis. Prolonged and stable hypertonia can sharply intensify and accelerate the atherosclerotic process, but it cannot induce it.

In the opinion of Perera (1960), there is no definite relation between high blood pressure and the development of atherosclerosis, although systematic observations show that the higher the diastolic pressure and the longer the time for which it is maintained, the poorer is the prognosis for the patient.

Barr et al. (1951) and V.T. Lyamtsev (1957) stressed the significance of the age factor, which determines the effect of hypertonia on the atherosclerotic process. According to Lyamtsev, the development of atherosclerosis at ages from 20 to 40 years is due chiefly to the appearance and progression of hypertonia. At ages above 40, the number of cases of atherosclerosis increases independently of hypertonia, and it is difficult to establish an influence of the latter. However, comparative data enabled the author to establish that atherosclerosis is three times more frequent when hypertonia is present than when blood pressure is normal.

In the opinion of A.L. Myasnikov (1949, 1954), a vascular neurosis due to disturbance of the CNS regulatory function lies at the base of hypertonia and atherosclerosis. Here the emergence of hypertonia may be due to dominance of vasomotor reactions. The author negates the possibility of a direct relation between atherosclerosis and hypertonia, because atherosclerotic changes develop even at normal arterial pressure. Only the atherosclerosis encountered in almost all cases in the later stages of the disease is a direct result of hypertonia. Nevertheless, hemodynamic disturbances and changes in the functional state of the vessel walls, which occur in hypertonia, influence the development of the atherosclerotic process when it arises against a background of metabolic displacements.

V.S. Smolenskiy (1960) observed ulcerous atherosclerosis of the aorta in 46% of persons with normal blood pressure and in almost 70% of cases with high blood pressure. A severe ulcerative process had occurred in 22% of patients with normal pressure and in 50% of the hypertonics. On the whole, extensive and severe aortic atherosclerosis was observed in just over half of the normotonics and in almost 90% of the hypertonics. The author concludes that high arterial pressure is a major factor in the de- /20 velopment of this severe form of atherosclerosis in the aorta. Similar results have been submitted by K.G. Volkova (1946, 1958), Ye.A. Livshits (1956, Ya.S. Goncharova (1957), V.S. Smolenskiy (1952), K.A. Gornak (1959), and other.

It was shown by the experimental work of K.G. Volkova (1953) and V.S. Smolenskiy (1953) that arterial hypertonia emerges as a predisposing factor because of the related tendency of the arteries to spasms, with the result that local trophic changes occur in the vascular wall. In their experiments, the authors reproduced various types of hypertensive states in rabbits (renal, reflexogenic, and coarctational) and fed them cholesterol. They established that the rabbit developed atherosclerotic vascular changes much less frequently with high and sometimes even unstable high arterial pressure than at normal pressure.

Simulating coarctation of the aorta, V.S. Smolenskiy observed that lipids accumulate more heavily at the location of the stenosis as compared with other areas of the aorta, even when the arterial pressure was not raised. This indicates that local hemodynamic disturbances create conditions for more manifest development of atherosclerotic changes. However, renal hypertonia, as Smolenskiy observed in a rather large number of cases, does not have an aggravating effect on atherosclerosis of the aorta, i.e., this form of hypertonia is not always the leading factor in the genesis of aortic atherosclerosis.

The experiments of V.S. Smolenskiy and K.G. Volkova confirmed the results of N.N. Anichkov (1925), who produced a sharp aggravation of cholesterol atherosclerosis of the aorta when the pressure in it was raised by constriction with a special pelotte, and when the rabbits were periodically suspended by their hind legs to increase pressure in the thoracic region. As a result of these experiments, he proposed a "combination" theory of atherosclerosis based on the combination of two factors – cholesterol and mechanical (i.e., elevated blood pressure) – in the pathogenesis of the illness.

Disturbance of vasa vasorum function is highly important in the development of atherosclerosis. S.S. Veil (1939) devoted much attention to its disturbances in hypertonia; these disturbances may emerge as a factor that intensifies the atherosclerotic process.

A.L. Myasnikov (1965) also attaches great importance to disturbance of vasa vasorum tonus in hypertonia [in] the development and intensification of the atherosclerotic process; in his opinion, this trophic factor is as important as the mechanical factor. /21

Later, A.L. Myasnikov states that hypertonic conditions may also contribute the development of atherosclerosis by strengthening the effect of the nervous mechanism underlying its pathogenesis.

Thus, the literature data on the effects of hypertonia on the development of atherosclerosis are contradictory.

In the opinion of A.L. Myasnikov (1965), the influence of atherosclerosis on arterial hypertonia is manifested in three ways.

Firstly, atherosclerosis of the major renal arteries results in ischemia of the renal tissue and the development of renal hypertonia of Goldblatt's type. If atherosclerosis begins while the hypertonia is still developing, it causes a sudden and stubborn exacerbation of the latter.

Secondly, localization of atheroscloerotic plaques in the zone of the carotid sinus also promotes the development of hypertonia.

Finally, the cerebral form of atherosclerosis tends to aggravate arterial hypertonia.

A.L. Myasnikov (1965) writes: "...it is difficult to accept either of the extreme positions on the mutual relationships between the two diseases: hypertonia is not the basis of atherosclerosis, nor is atherosclerosis the basis of hypertonia, although, as we have already noted, hypertonia undoubtedly influences the development of atherosclerosis, just as atherosclerosis undoubtedly influences the development of hypertonia."

A no less important question, but one that has been neglected, is that as to the influence of high-mountain factors on the course of atherosclerosis against a background of hypertonia.

N.N. Kipshidze (1959) made an interesting study of the effects of oxygen starvation on the development of experimental atherosclerosis.

This author concluded that, in combination with cholesterol in the diet of the animals, oxygen starvation causes more severe atherosclerosis of the aorta and coronary vessels than cholesterol feeding alone. According to this hypothesis, oxygen starvation would appear to disturb oxidative processes in the animal's organism, and this, in turn, affects assimilation and synthesis of exogenous cholesterol. Without ingestion of cholesterol, oxygen starvation produced only an insignificant increase in blood cholesterol content and did not result in the development of atherosclerosis.

The British investigator Altland (1960) studied the influence of pressure-chamber "altitude" (4900 m) on the development of atherosclerosis in rabbits. Macroscopic atherosclerotic changes in the aortas of both groups of rabbits decreased when they were held at "altitude," while microscopic changes in the pulmonary arteries and the degree of calcification of the aorta and other large vessels increased. /22

The studies of many authors have shown that different geographic localities whose populations differ in certain features of diet and mode of life are also found to differ in the frequency and severity of atherosclerotic damage.

Unequal blood-cholesterol levels have been observed by many foreign scientists in different population groups that differ in eating habits and the incidence of coronary disease. Malmors (1950) and Borgstrom (1960) found higher blood cholesterol contents among the population of Sweden, where fats account for 38% of caloric intake, and lower contents among Italians (20%). Italians living in Boston had higher blood cholesterol levels than those living in Naples, again in relation to the fat content of the diet (Miller et al., 1958). Similar relationships have also been reported from examination of various population groups in Guatemala (Mann, 1957), Israel (Brunner and Lobl, 1958), China (Ting et al., 1958), India (Padmavati et al., 1958), Yugoslavia (Zarcovic et al., 1955), and other countries.

High-fat diets are the rule in Great Britian and Finland (about 35%) (A. Keys, M.N. Keys, 1954; A. Keys et al., 1958) and in the USA (about 40%) (A. Keys, 1957). These investigators found a clear correlation between the percentage of the caloric intake accounted for by fats and blood cholesterol level: the highest blood cholesterol levels were reported in the USA and Finland, and the lowest ones among Bantu Negroes and Japanese. The latter were found to have high blood cholesterol (142 to 246 mg-%) depending on where they lived: the level was lowest among those living in Japan, somewhat higher among Japanese residents of Hawaii, and highest among those in Los Angeles; the fat percentage in the caloric intake increased in the same direction, from 10 to 40% (Keys, 1957).

In the USSR, the question as to the relation between the incidence of atherosclerosis and the population's diet was studied by I.S. Glazunov (1961). He made his examinations in four cities /23 situated in different geographic latitudes but similar in regard to population, administrative importance, and the occupational profile of the population: Tallin, Dushanbe, Ryazan', and Arkhangel'sk. The studies indicated that in Tallin, whose residents consume large quantities of animal fats and have higher blood cholesterol levels, the mortality rate from myocardial infarct is also higher. At Dushanbe, the diet is largely vegetarian with many green vegetables, and the inhibitants have lower blood cholesterol levels and, accordingly, lower mortality. Arkhangel'sk and Ryazan' occupied an intermediate position with regard to the indicators analyzed. Thus, it was found that blood cholesterol level and myocardial infarct mortality on the one hand are interrelated to the content of animal fats in the diet on the other.

This is also indicated by observations of I.N. Daraseliya (1962), according to whose data the transplanted population of

Sukhumi suffers from atherosclerosis of the coronary vessels at a rate double that for the natives; the basic cause of this disorder among the new residents was the fact that their diet contained fewer fresh fruits and vegetables and more animal fats than that of the lifelong inhabitants.

However, some authors negate the importance of ingested fats in the genesis of atherosclerosis, citing the Eskimos of Greenland, who eat large amounts of fats but are relatively seldom afflicted with atherosclerosis. As A.L. Myasnikov (1965) notes, Eskimos usually eat the fat of marine animals and fishes, and it may contain many unsaturated fatty acids, to which "antiatherogenic" properties are attributed.

Workers of the Don-Dog Therapeutics Institute of the USSR Academy of Medical Sciences (1958) who examined inhabitants of the Mongolian People's Republic reported that while their diet is rich in animal fats, their blood cholesterol levels are no different from those of residents of Moscow, and myocardial infarct is seldom observed.

Similar data were obtained by the Italian scientist Lapipirelli and coauthors, who studied the diet of Somali herdsmen. It was found that they drink 5-10 liters per day of camel's milk, which contains 71.7 g of fat per liter, but had low blood cholesterol levels. On this basis, the authors conclude that high-fat food is not the decisive factor in the emergence of atherosclerosis (cited from A.L. Myasnikov, 1965). /24

A.L. Myasnikov (1965) also notes that the amount of fat consumed is not always of decisive importance in the pathogenesis of atherosclerosis; it may merely contribute to it. It appears that atherosclerosis arises when the fats ingested with the food are out of proportion to metabolic conditions in the organism, and that this depends on the type of work done and the nervous and endocrine regulation of the systems.

In speaking of the importance of nutrition in the epidemiology of atherosclerosis, we must note that the frequency of the disease is different in different countries. Climate is a major factor.

According to White (1959), 843,410 of 1,555,000 deaths were due to diseases of the cardiovascular system, including 425,800 cases of coronary atherosclerosis and 179,110 cases of sclerosis of brain vessels.

The pathologists Vanga and Khu (1957) established in 885 autopsies, of which 816 were performed on Chinese and 69 on Europeans, that atherosclerosis is less conspicuous and appears later in Chinese than in Europeans; in their opinion, the difference is related to diet, the state of arterial pressure, the nervous system, and other factors.

Atherosclerosis is less common in southern countries. Guazzi (1956) found from autopsy data that atherosclerotic damage to the heart accounts for 42.6% of all cardiovascular defects in the USA, but only 6.1% in Italy.

A.S. Loginov (1942) reported from an examination of inhabitants of Ethiopia that atherosclerotic damage to the vessels is much less frequent there than in Europe and America.

Questions relating to the incidence of atherosclerosis among the population of Central Asia recently came under study. A.G. Glushchenko (1950) studied the frequency of atherosclerotic disease at Dushanbe. The work was done on post-mortem material (10,599 cadavers). The author determined that atherosclerosis is encountered less often among residents of Dushanbe than in other geographic localities. Only the initial forms of this disease were found among native residents, and no fatal cases were registered, while atherosclerosis was encountered more frequently among transplanted residents.

N.I. Tokar' (1959) analyzed autopsy material in the Pathological Anatomy Department of the Kirgiz State Medical Institute covering the period from 1940 through 1957 with the object of studying the frequency and peculiarities of development of atherosclerosis among the Kirgizian and European populations of Frunze (with consideration of age and sex). His data indicate that /25
atherosclerosis afflicts local residents extremely rarely.

Analysis of the material from the standpoint of age indicates that atherosclerosis makes its appearance much later along the native inhabitants.

A group of pathological anotomists at the Samarkand Medical Institute — A.I. Magrupov, Ye.N. Semenov, O.M. Azizova, T.M. Petrusheva, F.A. Abkhalinova, A.A. Rostovtseva, and S.A. Gamiyants (1964) — established in the study of autopsy material collected over 16 years (1947-1962) that the transplanted population was more than twice as susceptible to atherosclerosis (36.1%) than the native population (14.6%). The variations and frequency of atherosclerosis paralleled one another in the native and transplanted populations in different years.

M.M. Mirrakhimov (1964) also notes that certain forms of atherosclerosis are encountered very rarely among the native population. As for its frequency of occurrence among the native residents of Przheval'sk (1700 m) and newcomers, males among the latter suffer more frequently, while no differences were established among females.

On the basis of data from 1135 pathological-anatomical autopsies from various regions of Kirgiziya (local population and Europeans), L.S. Burmin (1963) reported that atherosclerosis is encountered 1.7 times as often among male Europeans in the 70-74-year age range than among male native residents, rarely among European females in the same age group, but 1.14 times as frequently at ages 75-79 than among native females. Transplanted males suffer more frequently from atherosclerosis than the females (44.4 and 41.1%), while native males develop it less frequently than females (22.5 and 33%).

The literature also contains information on the effects of a hot climate on the development of atherosclerosis.

M.Ya. Laufer (1962) states that coronary sclerosis is much less common among the native population of the Fergana Valley and the prognosis more optimistic than for immigrants.

Z.I. Umidova (1962) reported a comparatively low rate of atherosclerosis among rural inhabitants of the Surkhandarya Oblast'. She also noted lower blood cholesterol contents among these people as compared with residents of Moscow and Leningrad.

Yu.A. Atabekov (1963), who studied the incidence of atherosclerosis in the population of Tashkent, concluded that the climate of this city does not tend to lower the incidence of sclerotic damage to the cardiovascular system. /26

In the opinion of R.A. Abdullayev (1964), atherosclerosis affects the coronary vessels of both newcomers and "natives" without regard to nationality, and the clinical picture of the disease under the conditions of Uzbekistan is no different from that in other republics of the Soviet Union. He also states that the incidence of atherosclerotic damage to the vessels knows no geographic boundaries; its frequency depends on socioeconomic factors, the social and political atitudes of the people, and the nature of their diet.

In experimental studies of cholesterol atherosclerosis, M.Ya. Shchukina and S.B. Malyshev (1964) found from morphological examination of the organs of dogs that had received cholesterol and methylthiouracyl and been kept at an elevation of 3200 m for three months that the animals had a lesser tendency to atherosclerotic damage than did dogs kept under the lowland conditions of Frunze.

Chapter II /27

INFLUENCE OF THE MOUNTAIN CLIMATE ON THE AFFLICTED ORGANISM

An organism transferred from the climatic environment of the lowlands into the mountains naturally passes through a stage of acclimatization to the combination of meteorological (lower atmospheric pressure, changes in air temperature and relative humidity, amount of precipitation, winds, etc.) and heliogeophysical (strong solar and ultraviolet radiation, mountainous terrain, the peculiar variations of soil temperature in the mountains) factors. In this active biological process, which is based on purposive displacements in all functions of the organism, the central nervous system is the principal and regulating factor.

One specialist in alpine physiology, N.N. Sirotinin (1962), established that the relation between the basic nervous processes – stimulation and inhibition – undergoes changes even as a person ascends into the mountains (2000-4000 m).

Using a conditioned-reflex method, T.R. Ivakova (1963) established shifts in the higher nervous activity of rats during the first few days after they were transferred to a location high in the mountains (3200 m), in the form of a moderate inhibition with protective significance.

In the high mountains of Kirgiziya (3540 meters), N.V. Kantorovich (1963) observed that schizophrenics, epileptics, and manic-depressives undergo substantial psychomotor-activity changes during the first few days of exposure to the set of mountain-climate factors. It is noteworthy that the psychic changes in the schizophrenics formed the basis for the therapeutic effect of the alpine climate.

I.I. Ilipayev (1963), who used a conditioned-reflex method to study the dynamics of higher nervous activity in schizophrenics, established that the ratio of the fundamental nervous processes normalizes concurrently with their clinical convalescence.

The school of N.N. Sirotinin (1939) must also be accorded priority in establishing the beneficial nature of the alpine climate in allergic diseases (rheumatism and bronchial asthma), in whose genesis the central nervous system is thought to be an essential factor. /28

A.Z. Kolchinskaya (1964) observed a variety of higher nervous activity reactions to environmental conditions. She made studies under normal atmospheric pressure at Kiev in 1953-1954, and then organized a series of expeditions to various elevations on Mt.

El'brus: Adyl-Su Pass at 1700-2000 m, Terskol at 4200 m, Priyut Odinadsatyy Peak at 5300 m, and the saddle at the peak of the mountain.

On the first day after the trip into the mountains, which was made by train and then by automobile, the elation that was so distinct in the adults was not observed among the young people. Only some of them appeared to be excited.

An objective investigation of higher nervous activity among the young persons indicated marked disturbances in 36 out of 40 by the second or third day of the stay at 1700-2000 meters. They were manifested primarily in disinhibition of differentiations and of conditioned inhibition. In 19 subjects, a differential stimulus produced a motor reaction of the same magnitude as the positive conditioned stimulus, i.e., the differentiations were fully disinhibited, and they were no longer zero in 17 of the subjects. A conditioned inhibition did not produce the inhibitory reaction in 24 cases. The strength of the positive conditioned reaction had increased on the second and third days in 12 persons and decreased in 16, remaining unchanged in 12.

At these elevations, according to A.Z. Kolchinskaya, the higher nervous activity changes in adults manifest in a certain weakening of the inhibitory process; differentiations become incomplete, while the strength of positive conditioned reflexes increases in most cases, with a shorter latent period. During the first few days of a stay at 2000 m, adults are observed to be excitable as a result of a certain relaxation of internal inhibition.

The changes in higher nervous activity had subsided in most subjects (31 out of 40) by the tenth to fifteenth day at this altitude. The strength of positive conditioned reflexes remained the same as at normal atmospheric pressure, differentiations were restored, and conditioned inhibition was not disturbed.

Thus, we see from the results of A. Z. Kolchinskaya that the central nervous system responds first of all to the change in the environment and the relative deficiency of oxygen. Such reactions constitute one of the ways in which the organism adapts to new conditions of existence. The deflections of higher nervous activity in the mountains are temporary in nature and are of protective import. /29

All of these studies indicate that the acclimatization of the organism to mountain conditions is effected with participation of the central nervous system.

Naturally, an organism with a normally functioning central nervous system adapts more rapidly to new environmental conditions than an organism with CNS disturbances. In the mountains during the summer, under the influence of such beneficial climatic factors as strong solar and ultraviolet radiation, negative aeroionization, moderately warm and dry air, relatively constant low atmospheric pressure, etc., the organism's vitally important functions and protective-compensatory mechanisms are quickly strengthened. Even with periodic and abrupt fluctuations of weather factors in the mountains, healthy animals show no substantial deviations affecting circulation, respiration, or the nervous system. This is ensured by the healthy organism's regulatory mechanisms. In cases of "breakdown" (I.P. Pavlov), uncomfortable mountain weather conditions tend to complicate it.

Thus, the mountain climate factors may be classified as positive and negative in accordance with their effects on the organism. Sunshine and the ultraviolet radiation, which are very strong in the mountains, are basically positive (Z.Ya. Ryazantseva, 1959, 1962).

In moderate doses, ultraviolet rays have a normalizing effect on a number of pathological states. For example, it was found in our 1958-1960 studies that ultraviolet irradiation of rats with renal hypertonia usually lowers their blood pressure to normal. Cases have also been reported from practice in which ultraviolet rays have had a beneficial effect on the circulation in complex with numerous climatic factors (L.G. Filatova, M.M. Mirrakhimov).

The negative ionization of the air is another beneficial factor of the mountain climate. As far back as 1939, A.B. Bashno established high negative ionization of the air under the conditions of the "Issyk-Ata" health resort (1800 m) in Kirgiziya.

The view of aeroionization of negative sign as a factor beneficial to many morbid states is commonly encountered in the literature. /30

F.G. Portnov (1960) showed, with reference to a large body of material, that ionized-air therapy produces good results in hypertonia.

D.I. Panchenko (1962) observed that a high, stable concentration of negative ions (up to 1100 per cubic meter), together with other artificial meteorological factors operating in biotron tents produced hypotensive effects in hypertonia. It should be noted that the optimum temperature (18°C) and low air humidity (40%) were maintained at all times in the tents. In the mountains during the summer, temperatures are usually moderate and the air dry. Thus there is a basis for including these factors among those with a favorable influence on the pathological state that is hypertonia.

It can therefore be assumed that active solar and ultraviolet radiation, negative aeroionization, and the optimum combination of temperature and air humidity during the summer in the mountains may have a favorable influence on the course of a number of illnesses by stimulating the organism's compensatory mechanisms.

Let us dwell in greater detail on the question as to the response of the organism to lowered barometric pressure, which is one of the principal factors operating in the high mountains. We know that at normal pressure – 760 mm Hg – and the oxygen partial pressure that corresponds to it – 159 mm Hg – the blood in the capillaries of the lungs is adequately saturated with oxygen. At an elevation of 2000 m (596 ± 10 mm Hg), according to the accepted international table, the oxygen partial pressure in the inspired air decreases to 125 mm (as against the normal 159 mm Hg), while that in the alveolar air drops to 79 mm (compared to the usual 103 mm Hg). It may reach 69 mm Hg at an elevation of 3000 m.

N.N. Sirotinin (1939) established that instead of the normal 95% of oxygen, the arterial blood contains, on the average, only 89% under mountain conditions at 3000 meters, in both natives and immigrants.

In the opinion of A.A. Lavnikov (1961), ascent to elevations up to 2000 meters above sea level does not noticeably affect the way an individual feels. He calls this the neutral zone, and the zone from 2000 to 3000 meters the zone of complete compensation. In the compensation zone, according to A.A. Lavnikov, the organism begins to compensate for the oxygen deficiency in the inspired /31 air by intensified activity of the circulatory and respiratory apparatus. With these compensatory reactions on the part of the two systems, the organism is quite capable of dealing with the deficiency of oxygen in the air up to an elevation of 3000 meters. The author refers to 4000 meters as the disturbance threshold, and to 6000 meters as the critical threshold or critical zone.

Z.I. Barbashova (1960) submitted a more concrete interpretation of the mechanisms compensating for oxygen insufficiency and acclimatization of the organism to altitude. She distinguishes several steps in adaptation and acclimatization:

1. Adaptive reactions directed to maintenance of a constant oxygen partial pressure in the blood (reactions of the first kind).

2. Adaptive reactions directed to increasing tissue utilization of oxygen (reactions of the second order).

Z.I. Barbashova notes that the first-order reactions, whose purpose is to prevent a sharp drop in the blood oxygen partial pressure, cannot provide for acclimatization to altitude. The enhancement of circulation and pulmonary ventilation, the increase in blood oxygen capacity and blood minute volume – all of these adaptive reactions gradually subside. Z.I. Barbashova's many years of study under the supervision of A.G. Ginetsinskiy established the presence of second-order acclimatization reactions.

3. Enhancement of anaerobic energy-metabolism processes (third-order reactions).

4. An increase in the general resistance of the tissues (fourth-order reactions). It is known from the literature that adaptation to oxygen insufficiency is accompanied by a change in the organism's general resistance.

Under the conditions of the Kirgizian mountain climate (3540 meters), epileptic patients transferred from a foothill locality suffered fewer seizures (N.V. Kantorovich, 1963).

G.T. Pashayev (1962) observed later development and a milder course of experimental hepatitis induced in rabbits by carbon tetrachloride poisoning under the conditions of the "Isti-Su" health resort (2200 meters).

Pathophysiologists working at Yerevan obtained interesting data: on Mt. Aragats (3500 meters), clinical death required about 12 minutes, even after total blood loss, in altitude-acclimatized dogs. It was concluded from this that acclimatization of the or- /32
ganism to conditions of depressed oxygen partial pressure doubles the time of clinical death. Finally, data indicating slower development of the desoxycorticosterone (at 1800 and 3200 meters) and renal-desoxycorticosterone (3500 meters) forms of experimental hypertonia (M.A. Aliyev, 1963; S.I. Arestova, 1964) also support the existence of fourth-order reactions.

While distinguishing four types of adaptive and acclimatization mechanisms, Z.I. Barabashova takes note at the same time of unusual relationships among these compensatory reactions of the organism in the struggle for oxygen. For example, the first-order adaptive reactions are brought into play in the first stage of equilibration of the organism to the new environmental conditions, i.e., the respiratory and circulatory systems are activated. If the oxygen starvation is of short duration, the adaptive process may be limited to these reactions.

If, however, the lowered oxygen partial pressure in the inspired air becomes a long-term factor (as, for example, under mountain conditions), and if the partial pressure in the blood drops below normal in the presence of first-order compensatory reactions, then the struggle for oxygen is joined by second-order reactions, i.e., tissue oxidation-reduction processes, which are enabled to "work" at low partial pressure, thereby increasing the utilization of oxygen.

But what is the response of the organism to depressed oxygen partial pressure at elevations of 2000-3000 meters?

These elevations fall into the zone of complete compensation (A.A. Lavnikov, 1961). On the scale adopted (A.M. Charnyy, 1961), the oxygen partial pressure in the inspired air drops to 133 mm (as compared to the norm of 159 mm Hg) at 1500 meters, and that in the alveolar air to 82 mm (as against 102-107 mm Hg). The percentage saturation of the arterial blood drops from 96 to 92. The oxygen partial pressure in the inspired air is down to 110 mm and that in the alveolar air to 69 mm Hg at an elevation of 3000 meters. The percentage saturation of the arterial blood drops to 88%.

Thus, the phenomenon of relative oxygen insufficiency is naturally observed at elevations of 2000-3000 m.

There is no doubt that all of the adaptive-reaction types described above (I, II, III, IV) are inherent to the organism that finds itself under high-mountain conditions.

The human organism, which commands extensive biological possi- /33 bilities (in the sense of adaptation to environmental conditions), can easily handle the initial "irritating" effect of the mountain climate, its relative hypoxic effect on the organism.

The picture submitted by Z.I. Barbashova (1960) found confirmation in a large body of clinical-physiological material studied by M.M. Mirrakhimov (1964), who also recognizes the presence of a series of successive stages in the altitude acclimatization of the organism and attempts to interpret the significance of each of them with reference to human acclimatization to the mountains of central Tien-Shan as an example. He writes: "During the first phase of the acclimatization...the external respiratory function is enhanced, the minute and systolic heart volumes increase, as do bloodstream velocity, arterial pressure, and capillary permeability..." The author suggests that this period be called the phase of unstable acclimatization. Like Z.I. Barbashova (1960), who considers the first-order reaction to be a short-term one, M.M. Mirrakhimov regards the "unstable-acclimatization phase" as labile and "wasteful" because it requires increased consumption of oxidation energy.

M.M. Mirrakhimov called the next step in acclimatization the relative-stabilization stage. During this time, he assumes, the basic physiological functions return to normal. But the acclimatization process is not complete even now, since the stabilization of the physiological indicators is relative in nature.

He called the third phase the phase of complete stabilization. This stage in acclimatization to low oxygen partial pressure corresponds to Z.I. Barbashova's second-order reaction and also embraces the third- and fourth-order reactions.

It is in the light of these data from the physiology of the mountains that the literature descriptions of the influence of middle- and high-mountain conditions on the course of various diseases and pathological states should be interpreted.

Relief from bronchial asthma provided by the mountain climate. N.N. Sirotinin (1965) writes: "Acclimatization to the alpine climate may aid in the prevention of diseases involving oxygen insufficiency (bronchial asthma, anemia, hypertonia, myocardial infarct, dementia praecox). However, it can also be helpful in the treatment of these diseases." Sirotinin also expressed this view at the conferences on hypoxia at Kiev (1955-1964), /34
Frunze (1958), and Dushanbe (1963).

TABLE 1. STATE OF EXTERNAL RESPIRATORY FUNCTION IN ASTHMA PATIENTS IN THE FIRST FEW DAYS OF A STAY IN THE MOUNTAINS

Indicator	Level (M ± m)	Departure from initial level
Vital capacity	90.2	+10.8
Minute pulmonary ventilation	264.4	+65.2
Oxygen demand	161.3	+38.8
Pulmonary oxygen utilization coefficient	61.6	-2.7
Pulmonary ventilation limit	71.6	+13.3
Forced expiration rate	52.6	+8.9

S.P. Mel'nichuk (1963) made clinical-physiological observations on a group of bronchial asthma patients who were spending a month at an elevation of 2200 meters in the El'brus region. The results of the observations indicate that the alpine climate has a favorable effect on such patients: by the end of their stay in the mountains, 39 out of 44 patients had improved, three showed no change, and only two deteriorated slightly. After the return to Kislovodsk, a temporary relative deterioration of clinical state was observed in most of the patients, but it was followed by a stable and long-lasting improvement. Then, for periods ranging from a few months to a year and more, most of the bronchial asthma sufferers felt much better than they had in earlier years. Their fitness for work improved markedly, and some of them were for all practical purposes cured.

A study of external respiration made by S.P. Mel'nichuk on the day following the ascent to 2200 meters brought out definite changes in this function as well (Table 1).

In the author's opinion, the substantial increase in pulmonary ventilation minute volume and the rise in oxygen-demand level

together with a slight decrease in the coefficient of its utilization in the lungs, indicates that the respiratory apparatus of the bronchial asthma patients was functioning under stress during the first few days of acclimatization to alpine conditions. The marked increase in vital capacity, the pulmonary ventilation limit, and the rate of forced expiration indicate a distinct improvement in /35
the functional dilation of the bronchi and objectively confirm the statements of the patients to the effect that they could now breathe much more easily.

TABLE 2. STATE OF EXTERNAL RESPIRATION IN ASTHMA PATIENTS DURING THE FIRST FEW DAYS AFTER THEIR RETURN FROM THE EL'BRUS REGION

Indicator	Level (M ± m)	Departure from level in mountains	Departure from initial level
Vital capacity	89.1	-4.7	+9.7
Minute respiration frequency	15.0	-1.0	-2.5
Minute pulmonary ventilation	163.1	-60.4	-36.1
Oxygen demand	129.1	-22.1	+6.6
Oxygen utilization coefficient	79.9	+10.2	+15.6
Pulmonary ventilation limit	65.8	-12.1	+7.5
Forced expiration rate	60.8	+5.1	+17.1

During the subsequent stay in the mountains, vital capacity, pulmonary ventilation limit, and forced expiration rate increased over their initial levels, as well as by comparison with the first few days at altitude.

According to the data obtained, the work of the external (pulmonary) respiratory apparatus, which is most severely strained in bronchial asthmatics, improved substantially under the conditions of the alpine climate.

During the first few days after the return from the El'brus region, the external-respiration indicators of the asthma patients were much better than before the stay in the mountains (Table 2).

In the opinion of S.P. Mil'nichuk, the readjustment and improvement of external-respiratory regulation that takes place in the mountains is a major factor in the mechanism of the favorable therapeutic effect of the mountain climate on bronchial-asthma patients.

The author states that the vacation under the conditions of the alpine climate can be regarded as more than a symptomatic and temporary method of treating and preventing bronchial asthma: it is also pathogenetic and of prolonged effect.

Another investigator, A.A. Kochum'yan (1963), conducted observations at three different elevations: at Kislovodsk (800-850 m), at Terskol in the foothills of Mt. El'brus (2000 m), and at Novyy Krugozor (3000 m). /36

The camp to which the patients were taken was situated at the hamlet of Terskol between the valleys of the Terskol and Azau Rivers. The weather at the time was relatively chilly, with frequent heavy showers. Air temperature varied from +8 to +17°C during the early morning and evening, and from +16 to +25° during the day. The average atmospheric pressure was 589 mm.

During the first two days of their stay at Terskol, the condition of all patients of the first group deteriorated: the asthmatic attacks became more frequent and severe, and only on the third or fourth day did any improvement appear: the attacks stopped in three cases, and in two they became less frequent and less distressing than they had been at Kislovodsk.

The condition of five out of 17 patients in the second group deteriorated during the first two days: their asthmatic seizures became more severe. Twelve patients reported no subjective changes. Later, four out of the 17 patients experienced no further attacks, and the attacks were less frequent and milder in the other 13. The rattle vanished from the lungs of seven patients, and was reduced in six. Coughing and ejection of sputum stopped in eight patients and were reduced in one.

During the first few days, the pulse rates of the second group quickened by about 12-16 beats per minute, and the respiratory frequency increased by 1-3 per minute. The maximum arterial pressure increased by an average of 10-20 mm Hg, and the minimum by 5 mm Hg.

After two weeks at Terskol, 12 patients of the second group and two of the first were transferred to Novyy Krugozor (elevation 3000 m), where they spent six days.

The weather at Novyy Krugozor is much more severe than at Terskol, and its atmospheric pressure is substantially lower. The condition of two patients of the first group and 11 of the second group deteriorated at the 3000-meter elevation. The asthma attacks that had stopped at Terskol returned in some cases, and became even more severe in others. The rales returned, and the patients coughed and ejected sputum. With the turn for the worse, the patients were forced to resort frequently to various spasmolytics and to take them in large doses.

In addition, a number of signs of mountain sickness were reported among the patients at Novyy Krugozor: headache, dizziness, ringing in the ears, debility, nervous exhaustion, depression, and disturbed sleep. Almost all of them were quite out of breath even after light physical exertion. /37

The author explains the distress of the patients during the six-day stay at Novyy Krugozor as due to a sharper manifestation of hypoxia under the conditions of the lower atmospheric oxygen content, with the result that the inadequacy of the adaptive reactions of the cardiovascular and respiratory systems was made manifest. Another factor that was no less important in the author's opinion was the bad weather in this area (chilly temperatures with rain and fog).

From this, A.A. Kochum'yan concludes quite correctly that the condition of bronchial-asthma patients improves with increasing elevation only up to a certain point, and that the mechanism of the therapeutic effect of the alpine climate on such patients consists in the combined influence of a number of helpful factors operating in the mountains.

S.A. Ul'yanova and N.M. Shumitskaya (1963) report experiments in the treatment of bronchial-asthma patients by stepwise acclimatization to the mountain climate. For this purpose, they were driven to different elevations in the El'brus region — Novyy Krugozor (3000 m) and Peak "105" (3500 m), spending two days under observation at each point.

As a result of their observations of the patients, the authors established that prolonged residence (30 days) at elevations of 2000-3500 m above sea level has a favorable influence on the course of the disorder. Fourteen patients felt better: the frequency and intensity of the attacks diminished and bronchitic phenomena subsided. Four patients improved considerably. In two cases, the attacks that had been a daily event at Kislovodsk did not occur once in the mountains. The asthmatic condition that had persisted for a week or more before the expedition disappeared in the other two. These patients suffered mild attacks, but they were quickly brought under control with theophedrine, whereas at Kislovodsk it had been necessary to resort to adrenaline injections as many as 20 times a day.

In three cases, the stay in the mountains produced no appreciable improvement. In the author's opinion, this is explained by the fact that one patient had had pneumonia, while the condition of the other two deteriorated at the end of the expedition because of the cold and rainy weather. Only in one patient was /38
there a deterioration due to age (51 years) and the attendant disease (atherosclerosis of the brain and coronary vessels).

Laboratory scarification tests made before the expedition at Pyatigorsk and Kislovodsk by Ul'yanova and Shumitskaya showed that in those asthmatics in whom positive and weakly positive allergic reactions were observed 20 minutes and 24 hours after application of the allergens, these reactions diminished later with the ascent to altitude and with increasing time of residence in the mountains, with a gradual transition in most cases to negative. This is of definite practical importance, although most investigators still adhere to the allergenic theory of bronchial asthma. V.I. Krivoruk (1965) reports on the effectiveness of treating this disease under the conditions of the mountain climate (in the El'brus foothills).

In the opinion of V.G. Amatunyan (1965), the alpine climate (Dzhermuk) also has a therapeutic effect on emphysema. In the mountains, as compared with healthy individuals, emphysema patients show a substantial increase in ventilation, a decrease in HbO_2, and a more distinct wave of O_2 absorption and basal metabolism on the fourth to seventh days of the stay, persisting until the 15th-20th and 26th days. Basal metabolism frequently reaches above-normal values. The respiratory coefficient also increases. Basal metabolism declines in low-level emphysema.

Sanigenic and recidivistic effects of the alpine climate on cardiovascular pathology. A.D. Dzhaylobayev, S.I. Isakova, M.M. Mirrakhimov, and A.Yu. Tilis, who studied the effects of the mountains on cardiovascular diseases, showed that the external respiratory apparatus is functioning under greater stress even at 1650 m in cases of heart defects, and that the hemodynamic changes are also more pronounced. A certain increase in heart minute volume is observed at this elevation over the volumes at 2020 m and in the "lowlands."

V.T. Antonenko (1965) showed that when a schedule of acclimatization to the mountain climate is adhered to, the functional-compensatory possibilities of experimental rabbits with myocardial infarct are more pronounced under mountain conditions (El'brus) than in lowland areas (Kiev). A group of animals with "Terskol" (2000 m) infarct sustained hypoxic hypoxia in the mountains much better than did rabbits in which the infarct was produced at Kiev.

A.Yu. Tilis (1965) studies the influence of the alpine climate (3200 m) on the pathological state produced by loss of blood. /39 According to his data, the hemodynamic and oxygen-supply changes observed in dogs after a month in the mountains were more favorable than those in animals that were bled on the second or third day of residence under mountain conditions. These dogs sustain the circulatory effort quite easily (especially on the second day after bleeding), and this, together with the readjustments of other functional systems, contributes to a relatively good oxygen supply to the organism. After a month in the mountains, dogs were found to be better able to withstand blood loss under normal atmospheric pressure conditions.

The author and his coworkers were able to demonstrate even more clearly the stimulating influence of hypoxia in blood loss in the sense of activation of hemopoiesis under these conditions. It was found that when the animals were kept for a month at 3200 meters, much shorter times were required for regeneration and elimination of the aftereffects of anemia. As compared with a control (which suffered a severe blood loss – 3% of body weight), the times for recovery of the hematological indices at this elevation were reduced almost by half (13-14 days as against 23-25 at Frunze). These animals also had correspondingly shorter anemization periods with the attendant pronounced reticulocyte reaction of the blood and bone marrow.

In Tilis' opinion, the increase in erythropoiesis after hypoxic conditioning results from an increase in serum hemopoietic activity. In response to blood loss after a month in the mountains, the quantity of hemopoietins in the dogs increases by a factor of 15-20 as compared to the hemopoietic-activity increase of the control (at Frunze) to blood loss of the same severity.

The author states that hypoxic conditioning to blood loss has a stimulating effect on the organs that produce hemopoietic substances.

According to G.I. Kasymov, G.A. Gusseynov, and G.A. Guseyn-Zade (1965), preliminary acclimatization to altitude (2200 m) has a strong influence of the course and rate of recovery of metabolic processes in various forms of experimental anemia.

During the first few days after bleeding, both acclimatized and unacclimatized animals show increased cholesterol levels and lower sugar levels. There are sharp differences between their percentage contents.

The contents of the substances investigated nearly doubled in the acclimatized animals as compared to the levels in the unacclimatized ones. The significance of acclimatization is subsequently manifested even more clearly. While glycogen and sugar have returned to normal on the 16th day of anemization in the acclimatized animals, the process takes 30 days in the others. /40

On the basis of these data, the authors correctly recommend that the time of acclimatization to the mountain locality be taken into account in directing anemic patients to mountain health resorts.

The observations of P.Ya. Grinshteyn (1965) showed that hypertonia in persons living at a 3600-meter elevation proceeds at a lower arterial-pressure level as compared with that in patients at lower elevations.

Kirgizian scientists have done most of the work on the influence of the mountain climate on hypertonia.

The insignificant changes in bloodstream velocity, venous pressure, and pulse rate, the increased velocity and force of blood ejection at a somewhat lower arterial-pressure rise, the lower systolic index, and the absence of changes in the BKG index suggest, in the opinion of P.Ya. Grinshteyn, that "hypertonia is not characterized by a more severe course among inhabitants of the high mountains. The observed hemodynamic peculiarities in hypertonia at high elevations must be related not only to the basic pathological process, but also to the influence of the mountains."

We made a study of the features of the development and course of hypertonia under the conditions of the middle and high mountains over a number of years (1955-1965).

We first established distinctive features in the development of hypertonia under the conditions of the alpine climate. It was found that the climatic complex of the mountainous regions (1800, 2700, and 3200 m) retards appreciably the development of potential hypertonia with unilateral disturbance of renal blood circulation. However, this does not extend to that form of the disease that appears when both kidneys are affected. We therefore conclude that the optimum combination of mountain-climate factors in the summer retards the development of only the milder form of experimental hypertonia. To a certain degree, the mechanism of this effect is consistent with the nervous-reflex theory of the pathogenesis of renal hypertonia that was proposed by N.N. Gorev (1954-1959) and M.A. Kondratovich (1956).

It has been established that in animals with experimental renal hypertonia, the "vasomotor center is in a state of elevated excitability" (N.N. Gorev). /41

In the mountains (1800, 2700, and 3200 m), only unstable hypertensive displacements are observed during the first few days after suppression of one kidney, and they have disappeared within 1.5-2 weeks.

The nonappearance of any stable and persistent arterial-pressure increase in dogs subjected to dysfunction of the renal link in the regulation of vascular tonus in the mountains can be explained by the weak development of the pressor dominant in the vasomotor center. This is indicated, firstly, by the slow and unstable arterial-pressure rise after suppression of the kidney in the mountains. It is usually assumed that, in itself, a lengthy and stable arterial-pressure rise in experimental animals indicates the strength and inertia of the excitation process in the vasomotor center (M.A. Kondratovich). Secondly, an adrenalin pressor test made soon after ischemization of the kidney does not produce the typical vasoconstrictor reactions.

The development of a benign and milder form of hypertonia after suppression of one kidney and its severe form on suppression of both kidneys under alpine conditions is explained by two different mechanisms.

The rapid and progressive arterial-pressure rise immediately after suppression of the second kidney suggests triggering of a regulatory mechanism different from that in operation after suppression of the first, when the arterial pressure remains for the most part within the physiological range. The stable and maximal blood-pressure level observed following bilateral kidney suppression in the mountains appears to indicate a strong degree of dominance of the excitation process in the vasomotor center. This also explains the meteorotropic behavior of arterial pressure (step-function hypertension) in response to abrupt changes in the mountain-weather factors. A stagnant excitation focus on the dominant principle "attracts" all kinds of nonspecific pressor disturbances (low temperature, high air humidity, precipitation, electrical storms, etc.), and this stabilizes blood pressure at the high level. In unilateral kidney suppression, the weak pressor dominant (apparently supported by the effectiveness of the antihypertensive action of the mountain climatic and heliogeophysical factors when the contralateral kidney is still intact) /42 can correct the hypertensive shifts on changes in the mountain weather factors.

According to present-day conceptions, the mechanism of the pressor action of mineral corticoids — desoxycorticosterone and aldosterone — is related to the influence on electrolyte and water metabolism (V.V. Parin and F.Z. Meyerson, 1960).

We know that, unlike the glucocorticoids, DOCA increases the excitability of the brain, in an effect associated with a decrease in the intracellular sodium-iron concentration (Kolfer et al., 1947) with no change in intracellular potassium (Undberi and Daventort, 1949). However, electrolyte changes of this kind are not observed in other organs (muscle, heart, liver, blood, skin, etc.). When an excess of DOCA is administered, the intracellular sodium concentration increases and the potassium content decreases, not only in the brain, but also in the internal organs. It is this proportion of electrolytic ions that synergizes the sympathetic innervation and sensitizes the smooth muscles of the arterial vessels to catecholamines (Raab, 1952), with hypertonia as a result. During the period of relief from hypertension in the mountains, the blood shows no significant disturbance of the potassium-sodium ratio: the latter appears almost simultaneously with "disinhibition" of the desoxycorticosterone and renal-desoxycorticosterone hypertonia, with no changes in the potassium-ion level in either the plasma or the erythrocytes. This is a very important factor. If inhibition in the mountains coincides in time with relative stability of potassium in the erythrocytes, the potassium concentration in the brain must naturally remain normal. And it is no accident that the inhibition of the development of desoxycorticosterone hypertonia in rats in the mountains (3200 m) coincides with refinement and reinforcement of their cortical inhibition, i.e., with differentiation (M.A. Aliyev, 1965).

Transfer of animals with the benign mild form of hypertonia to a mountain locality (1800 m) with favorable climatic factors has a positive effect on its course. However, this "cure" of the hypertonia is temporary in nature. The general chill in the mountains results in a relapse into the hypertonic state. The "therapeutic shifts" in animals with the severe form of hypertonia (suppression of both kidneys) when they are moved to the mountains (2700 m) depends on the nature of the weather and climate factors. Thus, good weather promotes a progressive decrease in the arterial pressure in almost all animals. However, a sudden turn of the /43
weather for the worse causes a hypertonic relapse.

Transfer of the animals to higher elevations (3200 m) has different effects on the mild and severe forms of experimental renal hypertonia: the former, which arises after unilateral ischemization of a kidney, is "healed" (to judge from the blood pressure) more rapidly than the latter, which is produced by bilateral interference with renal circulation. Relapse into hypertonia on the variations of the mountain weather factors during the autumn is common to both.

The high mountains (3500 m) with their unstable weather and climate conditions have a less favorable effect on the course of renal hypertonia, and especially on its severe form. There are cases of "hypertonic crisis," which are sometimes fatal to the experimental animals. The pressor reaction to adrenelin and mesaton in dogs with renal and renal-hepatic forms of experimental hypertonia during the first few days of a stay under alpine conditions (2700-3200 m) is strongly inhibited; on the other hand, it is enhanced during the hypertonic relapse, especially in the autumn. The depressor reaction to nitroglycerine and Aminazine is enhanced markedly.

We concluded from experimental data that the sanigenic effect of the alpine climate on hypertonia is manifested only in the summer. Summer in the mountains, as compared with other seasons, is characterized by relative constancy of the weather factors, something that is of great importance for the organism afflicted with hypertonia.

During a second expedition (1965) into the Susamyr Valley (2700 m), we determined the influence of the mountain-climate factors on the course of the more severe form (suppression of both kidneys) of experimental hypertonia. The hypotensive effect was less pronounced and of shorter duration here. This is apparently explained on the one hand by the more stable character of the hypertonia and, on the other, by the unfavorable weather conditions during the summer of that year (low temperature, high air humidity, sharp barometric-pressure fluctuations, snow in the summer, strong winds, electrical storms, sunless days, etc.).

This hypothesis is confirmed by the results of clinical observations made over many years. Thus, V.Ya. Yurazh (1962) reports that hypertonia patients respond to a change in weather conditions with a rise in blood pressure and subjective symptoms characteristic of this particular illness (headaches, dizziness, cardialgia, /44 etc.). According to the author's observations, the strength of the meteorotropic pathological reactions depended on the suddenness, strength, and amplitude of the meteorological-factor fluctuations; at the same time, it was determined by the severity of the disease and the type of the patient's nervous system. The following observations of V.Ya. Yurazh are highly valuable. It was found that such a combination of weather conditions as low barometric pressure, high humidity, and strong winds had a particularly pathogenic effect. Even at 900 meters above sea level (foothills of the Zailiyskiy Ala-Tau), V.A. Sobolev (1964) observed an increase in arterial pressure and in the excitability of the vegetative division of the CNS in hypertonia in association with the deterioration in the weather conditions.

M.M. Mirrazhimov, A.U. Aytkulova, V.S. Dneprovskaya, A.A. Rayimbekova, and L.A. Khmel'nitskaya (1961), working at Frunze, also established a detrimental effect of high air humidity and atmospheric-pressure drops on hemodynamics in hypertonia and atherosclerosis.

It must be remembered that the combination of weather and climate factors operating in the mountains is not always detrimental. There are summers in which the combination of weather and heliogeophysical conditions is favorable (moderately warm, windless days with dry air and nights with refreshing breezes, relatively constant barometric pressure, no rainfall or electrical phenomena, strong solar and ultraviolet radiation, pronounced negative ionization of the air, etc.).

This optimum combination of weather and heliogeophysical factors favored the course of hypertonia in the mountains. Needless to say, the therapeutic effect of the mountain climate was more conspicuous in the milder form of the disease. For example, after unilateral interference with renal circulation, the drop in arterial pressure at the mountain locality was faster and quite conspicuous and long-lasting. In its severe form, hypotensive shifts intervened later and were of short duration.

The earlier arrival of autumn in the mountains changes the combination of weather factors sharply: temperature drops rapidly, humidity rises, the intensity of the solar and ultraviolet rays declines, and there are frequent drops in barometric pressure accompanied by precipitation.

Sharp changes in weather conditions produced "weather neuroses" in animals with hypertonia. Phenomena reminiscent of the "hypertonic crisis" were sometimes reported. Relapses were observed later during the stay of the animals in the mountains. /45

In view of the above, reference should be made to the potency of the biotron in regulating meteorological factors with the purpose of treating hypertonics. The essence of the therapeutic effect of the biotron is that for a certain time, it provides the sick organism with a combination of climate factors that promotes restoration of its protective forces (D.I. Panchenko, 1962). Thus, a stable barometric pressure is maintained in the biotron tents, eliminating the detrimental effect of pressure drops on the organism; air humidity is optimal, oxygen content is normal or, if necessary, increased, air temperature is constant, and the required ionization is provided; in addition, the patients are protected from noise, vibration, and electromagnetic radiation.

D.I. Panchenko notes correctly that "the helpful effect of climatic health resorts is based on restoration of adaptive apparatus, including the protective functions of the organism. However, even at the most ideal climatic health resort, the patient remains dependent on atmospheric fluctuations and other natural conditions." Insulation of the hypertonic from the unfavorable effects of atmospheric variations and "treatment in the biotron retards the development of hypertonia," "restores fitness for work to a substantial degree," and "prevents the threatening complications (infarct, cerebral hemorrhage, thromboses of the brain vessels) that are inherent in hypertonia." He observed an improvement in the condition of more than 1000 hypertonics who were treated in biotron tents and a decrease in their high blood pressure.

Regarding the mountain climate, it must be noted that the "biotronic" combination of weather factors may prevail during the summer. But the weather in the mountains is extremely unstable during the spring, fall, and winter, and it is not recommended that hypertonics, and especially those without mechanisms for adaptation to altitude, be sent to stay and rest in the mountains (2000 m and higher) during these times.

The authors (1963) analyzed 300 health-resort records of hypertonics who had been treated at the "Dzhety-Oguz" (2000 m) and "Issyk-Ata" (1800 m) health resorts in Kirgiziya. The results of the analysis showed, firstly, that the climatic and aerial-ionization therapy available at health resorts in the high mountains lowers blood pressure quickly and sharply and improves /46 the general condition of the patients; this therapeutic effect is pronounced during the summer and less distinct in the autumn and winter. Secondly, patients who came from localities at low and medium mountain elevations were better able to withstand the ascent and responded better to the sanigenic effects of the mountain-climate factors than those who came from the European part of the Soviet Union, Kazakhstan, and Uzbekistan.

The last decade has witnessed the first successful applications of climate therapy at some of the country's health resorts in the middle and high mountains (M.E. Efendiyev, S.M. Bedalova, and D.K. Akhundov, 1959; D.N. Istambekov, 1961; V.A. Breydo, T.N. Kazakova, A.Yu. Baskin, and L.G. Platsman, 1961).

On the above basis, we may conclude that mountain-climate factors assist the hypertonia sufferer out of his pathological state by stimulating the sanigenetic and restoring the vascular regulatory mechanisms.

Chapter III /47

FEATURES OF THE COURSE OF HYPERTONIA AS A BACKGROUND FOR SIMULATED HYPERCHOLESTEREMIA UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE

There are now many known methods for reproducing atherosclerosis of the arteries and coronary vessels in various species of laboratory animals. However, not all of them can be regarded as successful.

An important requirement in the design of models of atherosclerosis is that changes be produced in the vessels that correspond in localization, morphogenesis, and their basic biochemical indicators to the lesions that are typical for this disease in man.

Note is taken of the work of D.D. Krylov (1916) among the first investigations in the field of experimental coronary atherosclerosis in rabbits. When the animals were fed chicken-egg yolks or cholesterol dissolved in sunflower oil, he noted more or less distinct atherosclerotic changes in the small branches of the coronary arteries.

Feeding with cholesterol dissolved in sunflower oil was until recently a commonly used method of reproducing atherosclerosis in rabbits. It was shown by investigators at the Experimental Medicine Institute of the USSR Academy of Medical Sciences, working under the supervision of N.N. Anichkov, that atherosclerosis is modelled more successfully by repeated administration of 0.5 g of cholesterol in 10 ml of sunflower oil.

Each morning, the cholesterol solution is introduced into the empty stomach through a slender tube. After as few as 5-6 months, a substantial rise in the blood cholesterol content is observed in the rabbits, with accompanying sharp atherosclerotic changes not only in the aorta, but also in the coronary vessels. These changes, like the degree of hypercholesteremia, are manifest to different degrees in different rabbits (T.A. Sinitsina, 1953).

A simpler method of producing atherosclerosis in rabbits has /48
recently come into use: in the morning, on an empty stomach, they are fed cholesterol (1 g) mixed with 50 to 100 g of ground carrots (A.I. Mokhnacheva, 1950; M.A. Levchenko, 1956; N.A. Yushchenko, 1959), turnips (T.A. Sinitsina, T.N. Lovyagina, 1959; Moss and Dury, 1957; Masatelli, 1958), or cabbage (Sya-Zhen'-i, 1960). Atherosclerotic changes in the vessels are then observed within 2-3 months. This method is now generally accepted.

Other methods of producing atherosclerosis in rabbits are also known, but they are not widely used.

Rats are also used as atherosclerosis models. According to a number of authors, supplementary substances are needed in this case in addition to long-term cholesterol feeding. Many investigators (Hartroft et al., 1952; Wissler, 1954; Wilgram, 1954; Mallinov et al., 1954, 1956; Bragdon, 1952, 1957; Page and Brown, 1952) obtained high blood cholesterol levels and substantial changes in the coronary arteries when the rats were fed a high-cholesterol diet with choleic acids added to it. Morphologically, the changes in the arteries are atherosclerotic, and due to the deposition of lipids in the artery walls, but without "foam cells" or cellular infiltration. Mallinov (1954, 1956) produced changes in the arteries of rats as a result of experimental hypertonia induced by subjecting the animals to bilateral perinephritis simultaneously with cholesterol feeding.

In Wissler's experiments (1954), atherosclerosis was produced in rats only after hypertonia had been developed as a result of injections of desoxycorticosterone, antirenal serum, and salt and when they had been fed methylthiouracyl with cholesterol; atherosclerosis was produced in old rats that had been fed large quantites of fats over extended periods.

L.N. Lavrent'yev (1962) notes that rats that received a normal diet did not develop atherosclerosis on being fed cholesterol, but that pronounced atherosclerotic changes in the aorta appeared when the diet contained 5% cholesterol in addition to the amount of fat.

Various methods exist for reproducing atherosclerosis in rats, but none of them has as yet produced reliable results.

To clarify certain questions in the pathogenesis of atherosclerosis, experiments have also been performed recently to induce the disease in dogs, but a number of difficulties have been encountered and the results are not always positive. /49

While it is sufficient to feed rabbits cholesterol to develop hypercholesteremia and atherosclerosis, dogs require, in addition to prolonged cholesterol feeding, metabolic changes induced by suppressing thyroid function.

Steiner and Kendal (1946) proposed that the thyroid function of dogs be suppressed by introducing large amounts of methylthiouracyl (1.5 g) over the long term. To develop atherosclerosis in dogs, Lindsay (1952) removed the pituitary gland and then the thyroid; Gonsales (1956) gave intraperitoneal injections of radioactive iodine, and Chaikoff et al. (1941) and Marmorston et al. (1959) removed only the thyroid gland. At the same time, all these authors fed the dogs cholesterol dissolved in oil over extended periods.

The method proposed by Steiner and Kendal is regarded as most workable. Its essentials are as follows: before cholesterol feeding starts, the animals are given methylthiouracyl for three months (the dose is gradually increased to 1.5 g). Then, along with the methylthiouracyl, they are given 10 g of cholesterol dissolved in 40 ml of cottonseed oil. The experiment takes 52-54 weeks. As a result, the dogs develop hypercholesteremia (above 1000 against a norm of 90-120 mg-%) and severe atherosclerotic changes appear in the aorta and its major branch arteries.

T.A. Sinitsina (1964) modified this method slightly. Each day, without preliminary methylthiouracyl treatment, the dogs received 1.5 g of methylthiouracyl and 20-40 ml of a 12.5% cholesterol solution in oil through a stomach tube. In this method of inducing atherosclerosis in dogs, high hypercholesteremia develops within a month (more than 2000 mg-%), and atherosclerotic changes have appeared in the arteries in some of the animals within 6-8 months.

Steiner, Kendal, and Bevans (1949) experimented on three groups of dogs: animals of the first group were fed 1 g of methylthiouracyl mixed with their normal food each day for 14-15 months; cholesterol was dissolved in ether, mixed with the food, evaporated, and then given to the animals. The dogs of the third group were given methylthiouracyl in increasing doses: 0.8 g per day for two months, 1 g per day during the third month, and, beginning with /50 the fourth month and for twelve months, 1.2 g per day; 10 g of cholesterol was simultaneously added to the normal diet throughout the time of the experiment.

Pathoanatomical studies showed that the most distinct atherosclerotic changes developed in animals of the third group.

M.Ya. Shchukina (1966) modified this method slightly. Daily for four months, the dogs each received 1 g of methylthiouracyl and 1 g of cholesterol per kilogram of body weight. The preparations were administered with pluck sausage in the amount of 200 g per dog. After four months, the amount of methylthiouracyl was increased to 1.5 g per dog, and the amount of cholesterol to 1.5 g per kilogram of the animal's weight. Atherosclerotic changes in the aorta and coronary vessels were observed as soon as the sixth or seventh month.

The production of experimental atherosclerosis in dogs is of great importance. The data obtained on rabbits are not specific solely to this species of animal or to herbivorous animals in general; they may also be characteristic for other species, including carnivores. When atherosclerosis develops in dogs, in contrast to other animals, it is the major branches of the arteries of the heart and brain that are affected, thus permitting study of both the morphogenesis of the atherosclerotic changes and the functional disturbances that occur in atherosclerosis.

R.I. Kulakova performed experiments on middle-aged mongrol dogs of both sexes, since it has been reported (Lindsay, Chaikoff, and Jilmor, 1952) that old dogs may develop spontaneous changes in the cardiovascular system that simulate the changes in atherosclerosis.

Unlike many foreign and Soviet investigators, the present authors (1954-1964) were able to produce atherosclerosis in dogs against a background of incipient hypertonia (suppression of both kidneys), i.e., we made use of the hemodynamic-mechanical factor.

After establishment of stable hypertonia (about a month after ischemization of the second kidney), the animals were divided into three groups with consideration of weight, sex, and arterial-pressure level: the first group was the control; animals of the second group were given 1 g of methylthiouracyl per day for the first four months and 1.5 g per day during the subsequent 5 months; those of the third group were treated with methylthiouracyl (in the same amounts as in the second group) and cholesterol – 1 g apiece /51 for four months and then 1.5 g per kilogram of weight.

This type of experiment (hypertonia complicated by atherosclerosis) is of great significance: it permits study of the reciprocal relationships and pathogenetic links between two forms of complex cardiovascular pathology – hypertonia and atherosclerosis.

Course of hypertonia under "lowland" conditions (Frunze). After a stable arterial pressure had been established (systolic 118±4 mm, diastolic 73±7 mm), the left kidneys of the healthy animals were suppressed.

Suppression of one kidney resulted in the development of moderate hypertension. Thus, on the fifth day after the operation, the systolic pressure had risen by 43 mm ($p < 0.001$) and the diastolic pressure by 53 mm ($p < 0.001$). However, this rise was not stable; on the tenth day, the systolic pressure was down to 146±4 and the diastolic down to 93±4 mm Hg.

Fifteen days after ischemization of the left kidney, the experimental animals were subjected to the second operation – suppression of the contralateral right kidney, thus producing stable increases in both the systolic and diastolic pressures.

As early as the third day after ischemization of the second kidney, systolic pressure had risen to 186±8 ($p < 0.01$) and diastolic pressure to 138±9 mm Hg ($p < 0.01$); on the fifth day, both pressures were up sharply at 202±9 ($p < 0.001$) and 150±12 ($p < 0.01$). The pulse rates had decreased to 87±7 ($p < 0.02$) beats per minute. Thus, the additional visceral "shock" (suppression of the second kidney with its receptors) and activation of the renin-hypertensin-aldosterone system results in the emergence of a stable hypertonia (M.A. Aliyev, 1964). During the next ten days of its development, both the systolic and diastolic pressure indicators remained at a comparatively high level; at 15 days after ischemization of the second kidney, the systolic $M \pm m$ was 180±8 and the diastolic 138±8 mm Hg. Further observations over nine months were limited to daily recording of arterial pressure.

Dry hot weather arrived during the summer period of the investigation. In July, the daytime high temperature averaged 34.8° and the low 25°. In August, the daytime temperatures were somewhat lower: the maxima ranged up to 33.2°, and the minima to 21.7°.

The arterial pressure was somewhat higher than the initial value during July; however, this increase was statistically unreliable. /52 During the first half of August, systolic pressure dropped to 167±9 (initially 180±8) mm Hg. These hypotensive shifts correspond to the 36th-39th days of the development of the hypertonia. Later in August, arterial pressure rose markedly: the systolic value sometimes reached 212±24 and the diastolic value 127±9 mm Hg. This period is characterized by a slight drop in the daytime air temperature and atmospheric-pressure lows.

No sharp temperature or atmospheric-pressure fluctuations were observed at the beginning of September. As a result, the animals' systolic arterial pressures sometimes dropped by 10-11 mm. The latter half of September was rainy and the lowest daytime temperature was +6.8°C. The systolic pressures of the dogs rose to 220±17 and their diastolic pressures to 180±17 mm; hypertonic crises manifested in bleeding from the colon, paralysis of the hind legs, blindness, etc. were observed in some of the animals during this phase.

The October weather was similar to that of September; the temperature lows reached +3.8°C. Both the systolic and diastolic arterial pressures settled at levels above their initial values.

November was characterized by high humidity; snow fell at the end of the month and the temperature dropped to -16.5°C. As during the preceding months, the arterial pressures of the dogs remained at a high level: the systolic value varied from 183±14 to 220±0, and the diastolic value from 133±4 to 150±6 mm Hg.

During the winter (December, January, February), there were oscillations between subfreezing and above-freezing temperatures, and snow fell on some days. The minimum temperature in December was -11.7°C, and that in January -11.2°. During February, the daytime temperature rose, with occasional rain or snow. The lowest temperature was -2.6 and the highest +24°C.

During December, the arterial pressures remained above their initial values, but they were lower than the November data. The maximum systolic pressure was 193±4 mm and the maximum diastolic 133±14 mm; from time to time, the systolic pressure dropped to 180 and the diastolic to 120 mm Hg.

A drop in the systolic and diastolic pressures was recorded in January; in most cases it was found to be statistically reliable. On some days, the systolic pressure dropped by 30-40 mm Hg, and the diastolic pressure by 38 mm Hg. /53

In February, owing to the fact that the atmospheric-pressure and air-temperature fluctuations were sharper during the first half of the month than during the latter half, the systolic pressures exceeded the initial values by 10-13 mm Hg early in the month, while both the systolic and diastolic pressures dropped markedly during the latter part. The decrease sometimes amounted to 33 mm Hg.

There were no abrupt fluctuations in the weather factors during March and April. The first half of March was characterized by a decrease in the animals' arterial pressure to 150±8/105±6 mm. From March 5 through 9, the daytime air temperature was low and the atmospheric pressure high; the systolic pressure rose 15 mm. A tendency toward declining arterial pressure was observed during April.

Our data confirm the dependence of the course of hypertonia on seasonal weather conditions.

Course of hypertonia when modelled against a background of thyroid hypofunction under "lowland" conditions. It is known that methylthiouracyl suppresses thyroid function (B.S. Maksudov and L.A. Lushnikova, 1956). Thyroid function is also lowered during Stages II and III of hypertonia. This effect is evidently due to suppression of brain-cortex activity in the later stages of the disease, the development of sclerotic changes in the vessels of the brain, the thyroid itself, and the pituitary, with the resulting decrease in the production of thyrotropic hormone (A.M. Kolbasova, 1964; N.A. Terent'yeva, 1957). With this in mind, we cannot exclude a certain influence of the thyroid on arterial-pressure regulation.

In our experiments, the animals with thyroid hypofunction showed, during the latter half of July, a decrease in arterial pressure as compared to the initial value, and this decrease became statistically reliable on the 26th day (155±4; $p = 0.02$/102±6; $p = 0.01$). During the second month of methylthiouracyl treatment, there was also a drop in arterial pressure. Thus, the systolic pressure dropped to 160±0 ($p < 0.05$) and the diastolic pressure to 100±0 mm ($p < 0.001$) on the 21st of August.

Hypertensive shifts were observed in the latter half of September and in October. The systolic pressure rose to 233±12 ($p < 0.01$) and diastolic pressure to 163±10 mm ($p < 0.1$).

During the winter (sixth and seventh months of methylthiouracyl feeding), the systolic pressures gradually decreased; on certain days in January, the decrease amounted to 23±4 mm ($p < 0.05$). The diastolic pressure was down accordingly to 41±4 mm Hg ($p < 0.001$). /54

Progression of the hypotensive shifts was observed during March and April (the eighth and ninth months of the methylthiouracyl treatment); thus, on March 7, the pressure was down to 160±0($p < 0.05$)/107±8($p < 0.1$) as against an initial value of 180±8/138±8 mm Hg.

Thus, hypertonic animals with normal and hypofunctioning thyroid glands respond acutely to changes in the weather, but the course of the hypertonia is milder with developing thyroid hypofunction in spite of the uncomfortable weather conditions (winter months).

Information in the literature indicates that arterial pressure rises sharply when thyroid hormone accumulates in the organism (K.N. Georgiyevskiy, 1896, Ye.K. Prikhod'kova and K.M. Kalmykova, 1949; Ye.B. Grobovitskiy, 1952).

According to S.I. Kharlampovich (1960), the thyroid gland of the rabbit is in a state of hyperfunction during the first three months of experimental renal hypertonia.

By the sixth month of hypertonia, however, thyroid function has been inhibited substantially. Thus it was no accident in our experiments that the hypotensive shifts were more clearly in evidence precisely during the latter half of the 6-methylthiouracyl treatment period than at the beginning. At later stages in hypertonia, the hypoactive state of the thyroid is easily simulated (with 6-methylthiouracyl).

Course of hypertonia as a background for the modelling of thyroid hypofunction and alimentary hypercholesteremia under "lowland" conditions. Both systolic and diastolic pressures rise markedly with the course of time under the combined influence of the two factors – 6-methylthiouracyl and cholesterol. The largest arterial-pressure increase was registered on the 21st day of the treatment: 214±9($p < 0.02$)/$p < 0.25$ mm Hg. During the second month of observations, arterial pressure stabilized and varied in the range of the original values. On the 85th day (autumn), the hypertension maximum was observed at 226±8 ($p < 0.001$)/186±8 ($p < 0.001$) mm Hg.

During the fifth and sixth months of thyroid hypofunction and hypercholesteremia, the arterial pressure held at its maximum level – 210±10($p < 0.05$)/162±9($p < 0.01$) mm Hg. The atmospheric pressure and air humidity rose during this period, with frequent changes in temperature. /55

In animals with "pure" hypertonia, as we have noted, arterial pressure rises during this phase, but the hypertensive shifts are more distinct in the animals subjected to 6-methylthiouracyl and cholesterol treatment.

An insignificant drop in the arterial pressures (by 14 mm Hg systolic and diastolic) was observed at the end of the sixth and the beginning of the seventh month (January).

Arterial pressure remained at a high level during the spring months (eighth and ninth), but on some days it droped to moderate values (166±15/122±15 mm).

During this time, the hypertonia of the control animals was mild, without pressor shifts.

Thus, prolonged administration of exogenous cholesterol and 6-methylthiouracyl produces a more stable hypertonia and stabilizes it. This confirms the results of Ye.S. Gevondyan (1950), who observed a 20-25-mm Hg arterial-pressure rise in dogs while cholesterol was being administered.

Influence of the mountain climate on the course of hypertonia. A statistically reliable decrease in arterial pressure was noted during the first few days spent by the hypertonic animals in the mountains (2150 m). Thus, on the second day, the systolic arterial pressure dropped to 151±7 ($p < 0.01$) and the diastolic pressue to 110±5 mm Hg ($p = 0.05$).

On occasional days during the latter half of June, arterial pressure rose; it varied in the ranges 163±8/131±5 - 181±12/142±12 mm Hg.

During July, the daytime temperature rose (11-22°) and there was no precipitation. The arterial pressures remained at the previous level, but began to rise on 23 July (to 220±13($p < 0.01$)/166±±14($p < 0.05$) mm Hg).

This state of the animals persisted for a month – until August 22. During the next ten days, arterial pressure declined markedly (by 20/11 mm).

In September, the air temperature varied in the range from 13.5 to 2°C, and there was no precipitation. At the middle of the month, the arterial-pressure level had dropped to 153±8($p < 0.05$)//111±6($p < 0.05$) mm Hg.

In October, as in September, the weather remained relatively stable, and the arterial pressures varied from 163±6/128±10 to 195±6/157±5 mm Hg.

In November, air temperature dropped substantially (-15.5°C) and snow fell. It was at this time that a recidive arterial-pressure rise to 208±6($p < 0.01$)/163±6($p < 0.01$) mm Hg was observed. /56

Subfreezing temperatures and snowfalls prevailed in December and January. However, there were no pronounced pressor shifts.

Prolonged acclimatization (6-7 months) to the mountain conditions apparently promotes a more stable reaction of the adaptive mechanisms to the variable weather conditions, so that the winter discomfort factors do not produce hypertonic relapses. At the end of January and beginning of February, we even observed pronounced hypotensive shifts – 151±8($p < 0.01$)/151±9 ($p < 0.05$) mm.

Influence of the alpine climate on the course of hypertonia as a background for modelling of thyroid gland hypofunction. The question as to the effect of lowered barometric pressure on thyroid function has not been given adequate study. P.N. Veselkin (1942) and M.Ye. Vasilenko (1955) report that thyroidectomized animals show higher than normal stability to hypoxia. According to L.G. Filatova (1961), B.F. Malyshev (1958), I.K. Akhunbayev (1949), S. Turmambetov (1960), and Yu.V. Sergeyev (1963), men and animals placed under alpine conditions exhibit lowered metabolic levels and suppression of thyroid function.

Interest attaches to a study of the dynamics of arterial pressure and pulse in hypertonic animals with thyroid function suppressed by methylthiouracyl at an elevation of 2150 meters.

The combined effect of elevation and 6-methylthiouracyl, beginning on the second day of the stay in the mountains, causes a decrease in arterial pressure (144±12($p < 0.02$)/102±8($p < 0.05$) mm Hg). The first half of the month was characterized by hypotensive shifts. Pressor shifts coincident with electrical storms were observed from the second month.

More pronounced hypertensive shifts were reported during the third month of 6-methylthiouracyl treatment. Arterial pressure varied in the range from 180±12/131±10 to 212±14($p = 0.05$)/158±7 ($p < 0.05$) mm Hg. At the fourth month, it fell (to 168±8/130±5) and rose (to 200±10/152±20 mm Hg) by turns.

In October and November (fifth and sixth months), heavy snows fell and the barometric pressure fluctuated sharply. All of this had a unfavorable effect on the course of the hypertonia. The /57
arterial-pressure level rose to 214±8($p < 0.01$)/170±8($p < 0.01$) mm.

During the last two months of 6-methylthiouracyl treatment, arterial pressure remained at a high level: 182±13/140±11 - 205±5/162±5 mm Hg.

Thus, hypertonia took a more severe course in animals in which thyroid hypofunction was modelled in the mountains than among the control animals.

Influence of the alpine climate on the course of hypertonia as a background for modelling of thyroid hypofunction and alimentary hypercholesteremia. It is known that a decrease in thyroid function accelerates and intensifies the development of experimental atherosclerosis in rabbits; it is also the only condition under which experimental atherosclerosis can be induced in dogs and rats (T.A. Sinitsina, 1964; Shapiro, 1927; Steiner and Kendal, 1946; Bevans, 1951; Horlick and Katz, 1949, and others).

As in the preceding two groups, the dogs of this series showed distinct signs of hypertension during the first few months of their stay in the mountains. Even at the end of the first month of treatment, their arterial pressures showed a marked rise (to $177\pm\pm8/139\pm8$ mm Hg).

At the second month of cholesterol and methylthiouracyl feeding, there was no change in the course of the hypertonia: the systolic arterial pressures exceeded the initial values by only 2-5 mm Hg.

During the third month of cholesterol-6-methylthiouracyl treatment, the arterial pressure rose to $202\pm9 (p < 0.05)/160\pm7 (p = 0.01)$ mm Hg on certain days.

During the subsequent two months (4th and 5th), there were no regular variations in the course of the hypertonia. The arterial pressure fell (by 12-19 mm) and rose (by 11-12 mm Hg) by turns.

At the sixth month of treatment, the arterial pressure rose to $208\pm6 (p < 0.01)/161\pm4 (p < 0.01)$ mm Hg. During this month, the high presuure level was stabilized and there were no cases of hypotensive displacement.

During the seventh month of their stay in the mountains, the state of the animals was also characterized by progressing hypertonia; on certain days, their systolic pressures rose to 210 ± 10 ($p < 0.25$) and their diastolic pressures to $155\pm8 (p < 0.05)$ mm Hg.

During the last two months of the stay in the mountains, the course of the hypertonia took a turn for the better; on certain days, the systolic pressures were substantially lower.

Thus, hypertonia meets with no complications inthe mountains /58 (2150 meters) without the cholesterol and 6-methylthiouracyl treatment. Although the autumn and winter weather conditions induce a recidive arterial-pressure increase, there is nevertheless resistance to the unstable weather conditions in "pure" hypertonia.

When thyroid hypofunction develops as a result of excessive exogenous administration of methylthiouracyl, the hypertonia is at first mild (in the sense of the emergence of depressor shifts), but later, under prolonged treatment (up to 9 months) with methylthiouracyl and with the deterioration of the weather, the hypertonia progresses. The development of thyroid hypofunction and hypercholesteremia with hypertonia as a background causes no deterioration in the course of the hypertonia; when cholesterol is combined with 6-methylthiouracyl, the progression of the hypertonia is less pronounced than when only 6-methylthiouracyl is used.

Chapter IV /59

PECULIARITIES OF HYPERCHOLESTEREMIA AGAINST A BACKGROUND OF HYPERTONIA UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE

Changes in blood cholesterol content in animals with hypertonia under "lowland" conditions. Observations were made over nine months under "lowland" conditions (at Frunze). The animals with hypertonia were divided into three groups. The first group consisted of the control dogs (Pal'ma, Gertsog, Lipsi, Maska, Kalach, Laska); dogs of the second group were treated with methylthiouracyl (Venera, Lisa, Umnitsa, Tuzik, and Mazepa); animals of the third group were given cholesterol with methylthiouracyl (Dzhil'da, Lev, Osinka, Shalun, Gamma, Dinka, Zhuchka, and Ryzhik).

Let us first discuss the results obtained on dogs with "pure" hypertonia (the control group). During the summer and fall, these animals had average blood cholesterol levels that were basically within the normal range (see Table 3).

From the 30th through the 75th day, their systolic pressures were 10-37 mm high; their blood cholesterol levels also varied with a tendency to increase (by 37-54 mg-%).

A more or less sharp drop in arterial pressure (to the initial values) was noted on the 90th day; at about this time, the blood cholesterol levels were down to 115 (against an initial 134) mg-%.

During the winter months, blood cholesterol level varied with a tendency to increase, although this was not statistically reliable. There was not always a relation between arterial pressure and blood cholesterol. Thus, on the 138th day (during a cold spell), the arterial pressure remained at the initial level (183/ /133 mm), while the blood cholesterol level had increased by 67 mg-%. But on the 150th day there was an increase in cholesterol level (by 89 mg-%) in correspondence with an arterial-pressure rise (by 27 mm).

On the 210th day, when the daytime air temperature rose to +12°C, arterial pressure was down to 160/112 mm Hg. This was /60 accompanied by a decrease in blood cholesterol content to 167 mg-% (as against 201 mg-% during the cold period (when the temperature dropped to -5°C).

Thus, animals with experimental hypertonia showed their lowest blood cholesterol levels during the summer and autumn. In the winter and early spring, there was a tendency for it to rise (see Fig. 1).

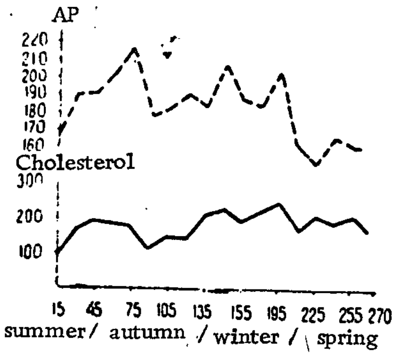

Figure 1. Seasonal Trends in Variation of Cholesterol Level and Arterial Pressure in Dogs with Hypertonia at Frunze.

We should note that a relationship emerges in hypertonia between arterial pressure and blood cholesterol level in most cases: when the arterial pressure rises (hypertensive shifts), the cholesterol content also increases (hypercholesteremia) and vice versa.

In the opinion of A.L. Myasnikov (1956), hypercholesteremia is one of the manifestations of disturbance to the humoral mechanisms characteristic of the later stages in hypertonia. It is also known (K.G. Urbanyuk, 1959; M. I. Zhidovtseva, 1959, and others) that disturbance of protein metabolism precedes the development of hypercholesteremia in hypertonia.

From this we might assume that there is a definite relationship in experimental hypertonia between hypertensive and hypercholesteremic shifts.

TABLE 3. VARIATIONS OF CHOLESTEROL LEVEL WITH ARTERIAL PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA UNDER "LOWLAND" CONDITIONS

Date	Day of observation	Cholesterol content, mg-% initial 134±4	Arterial pressure, mm Hg initial 180/138	Air temperature, atmospheric phenomena
1.VIII	15	105±15	170/127	32°
16.VIII	30	171±19	190/130	28°
31.VIII	45	186±21	192/132	29°
17.IX	60	182±15	202/160	29°, rain
3.X	75	176±24	217/173	17°
16.X	90	115±21	177/130	17°
30.X	105	147±27	183/123	5°, dew
15.XI	120	141±15	190/153	5°, frost
29.XI	135	201± 7	183/133	5°, frost, fog
17.XII	150	223±26	207/147	−8°, frost
2 I	165	192±31	187/127	−4°, frost
14 I	180	218±48	183/137	−7°, frost
1.II	195	243±86	203/137	2°, fog
18 II	210	167±15	160/112	12°, fog
4 III	225	205±90	150/105	4°, rain
18 III	240	189±65	165/120	5°, dew, fog
1 IV	255	201±46	160/110	13°, rain
15 IV	270	156±14	160/110	8°, rain

Variation of blood cholesterol content in animals with hypertonia and thyroid hypofunction under "lowland" conditions. We know that a lowering of metabolism by suppression of thyroid function (with uracyl and methylthiouracyl) results in aggravation of alimentary hypercholesteremia and atherosclerosis in rabbits (T.A. Sinitsina, 1953). /61

We attempted to establish a correlation between the hypofunctional state of the thyroid gland caused by methylthiouracyl and the extent of the change in lipid metabolism in hypertonic dogs (as compared with "pure" hypertonia).

TABLE 4. VARIATIONS OF CHOLESTEROL LEVEL AS A FUNCTION OF ARTERIAL PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA ON SUPPRESSION OF THYROID FUNCTION UNDER "LOWLAND" CONDITIONS

Date	Day of observation	Cholesterol content, mg-%	Arterial pressure, mm Hg	Air temperature, atmospheric phenomena
		initial 134±4	initial 180/138	
1.VIII	15	121±33	190/143	32°
16.VIII	30	200±35	200/142	28°
31.VIII	45	239±95	175/115	29°
17.IX	60	215±22, $p<0{,}01$	192/155	29°, rain
3.X	75	216±24, $p<0{,}01$	190/140	17°
16.X	105	165±33	180/123	5°, dew
15.X	120	149±29	190/126	5°, frost
20.XI	135	198±46	187/140	—8°, frost
17.XII	150	167±56	187/140	—8°, frost
2.I	165	187±19, $p<0{,}02$	166/110	—4°, frost
14.I	180	293±37, $p=0{,}002$	177/117	—7°, frost
1.II	195	263±57, $p=0{,}05$	173/117	2°, fog
18.II	210	309±32, $p<0{,}001$	183/127	12°, fog
4.III	225	291±33, $p<0{,}002$	180/120	4°, rain
18.III	240	208±61	173/137	15°, dew, fog
1.IV	255	236±21, $p<0{,}001$	173/117	13°, rain
15.IV	270	232±9, $p<0{,}001$		8°, rain

As we see from Table 4, as soon as two weeks after the start of the methylthiouracyl treatment, the hypertonic dogs showed some decrease in cholesterol content, but then the cholesteremia increased markedly. A reliable increase in cholesterol content was noted on the 60th and 75th days of observation (averaging 81-82 mg-%), but arterial pressure increased insignificantly (by 10-12 mm).

During the autumn months (from the 90th through the 150th day of the 6-methylthiouracyl treatment), the dogs showed a /62

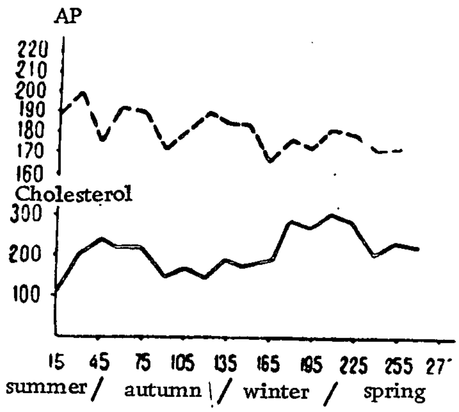

Figure 2. Seasonal Trends in Variation of Cholesterol and Arterial Pressure in Dogs with Hypertonia on Suppression of Thyroid Function with Hyperlipemia under the Conditions of Frunze.

tendency to lower blood cholesterol levels. Their arterial pressures varied in the initial range.

During the winter and spring (days 165 through 270), a reliable increase in blood cholesterol level was observed (from 187 to 309 mg-%). Despite the comparatively mild course taken by the hypertonia (the arterial pressure varied in the initial range), cholesterol content rose during this period (see Fig. 2).

Thus, it was not always possible to detect a relation between arterial-pressure level and blood cholesterol content in the animals with hypertonia and suppressed thyroid function.

Variation of blood cholesterol level in dogs with hypertonia on suppression of thyroid function with alimentary hypercholesteremia under "lowland" conditions. It was stated above that cholesterol is the most important factor in the etiopathogenesis of atherosclerosis. Cholesterol-containing protein-lipid complexes are carried by the blood to the intact in the lining of the artery and infiltrate the nonvascular intima to form lipoid plaques. The process advances in undulant fashion, activation alternating with subsidence; there may even be so gross /63 a change in the reactively expanding tissue of the vessels as reversed development of the process (V.V. Tatarskiy, V.D. Tsinzerling, 1950; N.N. Anichkov and K.G. Volkova, 1955; T.A. Sinitsina, 1955, and others).

Removal of the thyroid or suppression of its hormone-producing function by chemical agents accelerates the development of experimental cholesterol atherosclerosis (A.L. Myasnikov, 1965).

According to our data (see Table 5), blood cholesterol content doubled in all dogs during the first two weeks, after which the hypercholesteremia maintained a relatively stable level. On the 30th day, the average cholesterol level reached 376 mg-%; the dog Zhuchka showed 406 mg-% and Osinka 700.

The highest cholesterol level was observed on the 45th day: 589 mg-%, which is more than four times the initial level. The /64 arterial pressure was stable at a comparatively high level (183/ /123 mm Hg).

TABLE 5. VARIATIONS OF BLOOD CHOLESTEROL LEVEL AS A FUNCTION OF BLOOD PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA, THYRIOD-FUNCTION SUPPRESSION, AND ALIMENTARY HYPER-CHOLESTEREMIA UNDER "LOWLAND" CONDITIONS

Date	Day of observation	Cholesterol content, mg-%	Arterial pressure, mm Hg	Air temperature, atmospheric phenomena
		initial 134±4	initial 180/138	
1.VIII	15	269±30, p<0,001	198/151	32°
16.VIII	30	376±49, p<0,001	185/120	28°
31.VIII	45	589±32, p<0.001	183/123	29°
17.IX	60	371±52, p<0,001	201/158	29°, rain
3.X	75	412±50, p<0,001	210/160	17°
16.X	90	442±26, p<0,001	211/155	17°
30.X	105	367±34, p<0,001	211/160	5° dew
15.XI	120	378±22, p<0,001	207/155	−5°, frost, fog
29.XI	135	487±51, p<0,001	193/147	−5°, frost
17.XII	150	544±76, p<0,001	198/154	−8°, frost
2.I	165	296±48, p<0,001	198/138	−4°, frost
14.I	180	704±56, p<0,001	198/144	−7°, frost
1.II	195	810±86, p<0,001	200/142	2°, fog
18.II	210	791±91, p<0,001	190/150	12° fog
4.III	225	1572±398, p<0,01	202/138	4°, rain, fog
18.III	240	372±144	196/154	15°, frost, fog
1.IV	255	482±102, p<0,01	184/144	13°, rain
15.IV	270	585±90 p<0,001		8°, rain

From the 60th through the 120th day of treatment with cholesterol and 6-methylthiouracyl, the cholesterol level varied in the range from 371 to 44 mg-% in some of the dogs (for example, Gamma). The average content on the 75th day was 632 mg-%.

During the winter, blood cholesterol levels rose substantially and remained high for a long time. Thus, the average cholesterol level reached 926 mg-% on the 165th day. The highest levels were noted in the dogs Gamma (1030) and Osinka (2514 mg-%). Their arterial pressures rose by 10-23 mm Hg.

The highest blood cholesterol content registered over the entire time of the observations was 1572 mg-% on the 225th day. The /65 dogs with the highest levels on this day were Gamma (2028), Shalun (2308), and Dzhil'da (2270 mg-%). The arterial-pressure level was 202/138 mm Hg.

The high cholesterol level gave way suddenly to a low level (dropping from 1572 to 372 mg-%); during this period (from March 4 through 18), the air temperature rose from 4 to 15°C.

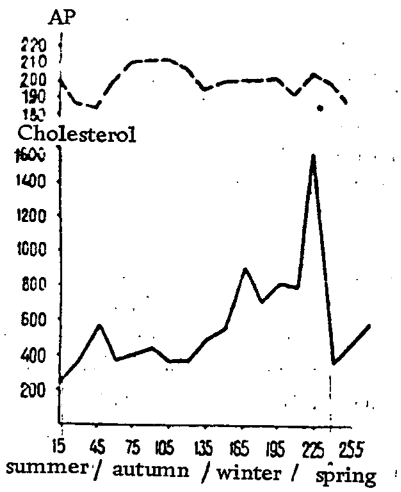

Figure 3. Seasonal Trends in Variation of Cholesterol and Arterial Pressure in Dogs with Hypertonia, Thyroid-Function Suppression, and Hyperlipemia under the Conditions of Frunze.

By the ninth month (spring) of administration of cholesterol to the animals in combination with methylthiouracyl, the cholesterol levels were up slightly, but still much lower than during the winter months (see Fig. 3).

N.G. Yastrebtsova, K.A. Gornak, E.A. Klyandzhuntsev, N.A. Makarov, and T.R. Shmul'yan (1961), who produced cholesterol atherosclerosis in dogs, reported the greatest cholesterol-content increase in animals in which the renal (renovascular according to B.V. Petrovskiy, 1966) model of hypertonia had first been induced.

However, to judge from the data of these authors, the cholesterol level increased insignificantly (350-413 mg-%) in hypertonia with choles- /66
terol treatment as compared with our data (582-600 mg-%).

In the experiments of M.Ya. Shchukina (1965), who produced atherosclerosis in healthy dogs at Frunze, the cholesterol level varied in the range from 258 to 316 mg-% during the first three months, while in our experiments the blood cholesterol levels of the hypertonic dogs were at 269-589 mg-% during this period.

Thus, the rise in the cholesterol level is more pronounced in hypertonia with thyroid function suppression (6-MTU) and alimentary hypercholesteremia (cholesterol feeding) than it is in "pure" hypertonia. Table 6 presents comparative data from the three series of studies.

Variation of lecithin content and lecithin-cholesterol coefficient in dogs with hypertonia, thyroid function suppression, and alimentary hypercholesteremia under "lowland" conditions. In the group I animals ("pure" hypertonia), lecithin content varied with- /67
in the initial range (see Table 7), sometimes exceeding it, during the first 45 days. However, it showed a reliable increase on the 60th and 70th days (to 479-507 as compared to the original 364 mg-%). During subsequent months, its level in the blood remained within the physiologically normal range, although it sometimes rose or fell, reaching 280 and 427 mg-%.

Thus, the lecithin level undergoes no significant changes in animals with "pure" hypertonia.

TABLE 6. AVERAGE CHOLESTEROL LEVELS IN BLOOD OF DOGS UNDER "LOWLAND" CONDITIONS (in mg-%)

Day of obser-vation	Group: I (hypertonia)	II (hypertonia + 6-MTU)	III (hypertonia + 6-MTU + Chol.)
15	105±15	121±33	269±30, p<0,001
30	171±19	209±35, p<0,05	376±49, p<0,01
45	186±21	239±95	589±32, p<0,05
60	182±15	215±22	371±52, p<0,01
75	176±24	216±24	412±50, p<0,01
90	115±21	143±14	442±26, p<0,001
105	147±27	165±33	367±34, p<0,001
120	141±15	149±29	378±22, p<0,001
135	201±7,0	198±46	487±51, p<0,001
150	223±26	167±46	544±76, p<0,01
165	192±31	187±19	926±118, p<0,01
180	218±48	293±37	704±56, p<0,01
195	243±86	263±57	810±86, p<0,01
210	167±15	909±32, p<0,01	791±91, p<0,01
225	205±90	291±33, p<0,05	1072±398, p<0,02
240	189±65	208±61	372±144, p<0,05
255	201±46	236±21	482±102, p<0,01
270	156±14	232±9	585±90, p<0,001

TABLE 7. VARIATION OF LECITHIN CONTENT IN BLOOD OF DOGS (INITIAL CONTENT 364 23) UNDER "LOWLAND" CONDITIONS, IN mg-%

Date	Day of obser-vation	Group: I (hypertonia)	II (hypertonia + 6-MTU)	III (hypertonia + 6-MTU + Chol.)
1.VIII	15	327±65	388±92	614±190 p<0,05
16.VIII	30	410±41	505±66	726±74, p<0,001
31.VIII	45	451±59	477±53	787±84, p<0,001
17.IX	60	479±35, p<0,02	633±82, p< 0,001	730±76, p<0,001
3.X	75	507±41, p<0,01	423±28	712±59, p<0,001
16.X	90	280±48	493±25, p<0,01	804±43, p<0,001
30.X	105	427±53	357±110	512±49, p<0,02
15.XI	120	413±13	497±55, p<0,05	729±71, p<0,001
29.XI	135	398±25	508±51, p<0,05	868±83, p<0,001
17.XII	150	380±52	395±82	950±96, p<0,001
2.I	165	363±51	360±27	807±100, p<0,001
1.II	180	425±37	512±62, p=0,05	642±120, p<0,01
18.II	195	285±55	500±30, p=0,001	578±210
4.III	210	335±56	487±31, p=0,01	499±60
18.III	225	295±42	510±50, p<0,02	700±203
1.IV	240	275±44	265±28, p<0,02	351±67
15.IV	255	325±25	330±52	369±34
	270	295±36	343±51	552±136

In the group II dogs (6-methylthiouracyl treatment), there was a tendency for lecithin content to increase from 15th day, although this was not statistically certain for the first 45 days. On the 60th day, the amount had reached 633 mg-%, but it dropped off noticeably from the 75th through the 165th day (to 357 mg-%). From the 180th through the 240th day, the lecithin level rose, but later it dropped to below its initial value.

The lecithin level in group III animals (cholesterol and methylthiouracyl) nearly doubled from the 15th day. The statistically reliable increase persisted through the 180th day, varying in the 512-868-mg-% range. However, from the 195th day, despite the high blood cholesterol level, the lecithin level began to decrease. In subsequent months, the lecithin levels of the group III dogs lagged behing their cholesterol levels. Lecithin varied from 351 to 950 as against 280-507 mg-% in the controls. /68

Attention should also be drawn to the variations of the lecithin-cholesterol ratio.

As we see from Table 8, this index did not change in the animals with hypertonia (group I) from the beginning of the observations to the 120th day; it remained for the most part within the initial range. Reliable decreases were noted on the 135th, 165th, 180th, and 225th days of observation. On subsequent days, it held nearly at the initial level.

Nor were there any particular variations in the lecithin-cholesterol ratio of the group II animals (from the 15th through the 150th days); only on the 75th day did it drop to 1.96 ($p < 0.05$), varying from 1.2 to 2.9 on the other days.

In the animals of this group, therefore, a tendency to decreasing lecithin-cholesterol ratios was observed at the end of

TABLE 8. VARIATIONS OF LECITHIN-CHOLESTEROL COEFFICIENT (INITIAL VALUE 288±0.3) UNDER "LOWLAND" CONDITIONS

Day of observation	Group: I (hypertonia)		II (hypertonia + 6-MTU)		III (hypertonia + 6-MTU + Chol.)	
15	3,05±0,49		3,1 ±0,57		2,37±0,24	
30	2,39±0,09		2,42±0,24		1,99±0,14,	p<0,02
45	2,42±0,12		3,17±0,9		1,85±0,15,	p<0,02
60	2,66±0,13		2,48±0,57		18,9±0,24,	p<0,02
75	2,95±0.32		1,96±0,18,	p<0,05	1,77±0,13,	p<0,01
90	2,66±0,82		2,53±0,95		1,83±0,1,	p<0,01
105	2,99±0,4		2,78±0,95		1,76±0,37,	p<0,01
120	2,97±0,27		3,23±0,63		1,94±0,21	
135	1,63±0,08,	p<0,001	2,65±0,16		1,78±0,13,	p<0,01
150	2.60±0,17		3,03±0,71		1,8 ±0,19,	p<0,01
165	1,91±0,05,	p<0,01	1,65±0,17,	p<0,01	1,44±0,44,	p<0,01
180	1,99±0,27,	p<0,01	2,32±0,45		1,2 ±0,27,	p<0,001
195	2,00±0,47		2,09±0,49,	p<0,01	0,72±0,18,	p<0,001
210	2,95±0,03		1,48±0,06,	p<0,01	0,9 ±0,27,	p<0,001
225	1,81±0,05,	p<0,001	1,72±0,03	p<0,05	0,5±0,11	p<0,001
240	2,46±0,5		1,2 ±0,33,	p<0,001	0,94±0,24,	p<0,001
255	2,81±0,6		1,43±0,64,	p<0,01	0,77±0,7,	p<0,001
270	2,9 ±0,03		1,57±0,3,	p<0,001	0,99±0,12,	p<0,001

the period of the observations. It was found that the blood cholesterol content increased more sharply than the lecithin level in the hypertonic dogs receiving methylthiouracyl, with the obvious result that this coefficient decreased.

In the group III animals, which received cholesterol and methylthiouracyl, the lecithin-cholesterol ratio decreased, though slowly, as the experiment continued. It ranged from 1.77 to 2.37 from the 15th through the 120th day.

The later period (from the 135th through the 180th day) was characterized by a more pronounced decline of this coefficient (from 1.2 to 1.94).

During the last three months, the lecithin-cholesterol ratio varied in the range from 0.5 to 0.99.

As the data in Table 8 show, the fluctuations of this coefficient in groups I and II remained within the physiologically normal range from the 15th through the 195th day of observations (from 1.91 to 3.05 and from 1.65 to 3.32). During the last 2.5 months, however, it showed a reliable decrease to the 1.2-1.72 level in the animals receiving methylthiouracyl.

A distinct tendency for this indicator to decrease was noted in the group III dogs. This trend was especially pronounced during the last three months.

The decrease in the lecithin-cholesterol ratio was evidently due to the increase in blood cholesterol level while the lecithin /69 level remained relatively constant. It was established that the ratio declines in cholesterol atherosclerosis, and that the degree of lipid accumulation in the aorta depends to a substantial degree on the lecithin-to-cholesterol ratio (M.V. Bavina, 1951; Kellner, Correl, Ladd, 1951).

Variation of blood cholesterol content in animals with hypertonia under mountain-climate conditions. One of the early studies of lipid metabolism under high-elevation conditions was made by Robeno in 1926. Examining his own blood and the blood of dogs and guinea pigs at Turin (elevation 2000 m), he established that the contents of fat and cholesterol were higher in the mountains, while phosphatide levels remained unchanged. Robeno considered not only the rarefied air, but also the low temperature as the causes of these changes.

A.Ya. Shurygin (1962) observed a tendency to hypercholesteremia in hypertonic patients (of degrees II and III) under the conditions of a 1750-meter elevation.

M.Ya. Shchukina (1964) reported an increase in cholesterol in /70 dogs given cholesterol and methylthiouracyl in the mountains (3200 m).

Our experimental hypertonic dogs were divided into three groups: dogs with "pure" hypertonia formed the first group (Volna, Seraya, Pegiy, Zhuchok, Kobra, Dzheri, Gazel'); animals of the second group (Krasavitsa, Kashtan, Vityaz', Astra, Dinara, Pamir) were given methylthiouracyl in the mountains (2150 m), and those of the third group (Romashka, Arma, Chernaya, Sil'va, Pushinka, Rybak, Yasnaya, Volchok, Veter, Alisa) were given both cholesterol and methylthiouracyl.

Let us first discuss the data obtained on the dogs with "pure" hypertonia that were transported to the mountains (2150 m) as a control. We see from Table 9 that their blood cholesterol levels had risen to 204 as against the initial 148 mg-% after as few as 15 days. Arterial pressure decreased to 163/125 as against the initial 180/129 mm Hg. During the summer and autumn period (until November 2), the cholesterol level was slightly above its initial value, but for the most part it varied in the range from 149 to 203 mg-%, while arterial pressure held at the level 163/125 -193/153 mm Hg.

During the winter and spring, the blood cholesterol levels rose by comparison not only with the initial value, but also with the content during the summer and fall, varying in the range 177-

TABLE 9. VARIATIONS OF CHOLESTEROL CONTENT AS A FUNCTION OF ARTERIAL PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE (2150 m)

Date	Day of observation	Cholesterol content, mg-%	Arterial pressure, mm Hg	Air temperature, atmospheric phenomena
		initial 148 ± 9	initial 180/129	
5.IV	15	204±67	163/125	21, fog, rain
20.IV	30	176±48	168/125	16°
5.VIII	45	153±9	179/133	17°
19.VIII	60	149±32	180/139	22°
5.VIII	75	159±33	160/131	16°, rain, fog
19.VIII	90	188±48	164/145	20°
4.IX	105	181±60	193/153	13°
22.IX	120	172±41	190/153	18°
7.X	135	157±38	176/133	16°
23.X	150	156±50	181/141	2°, windy
2.XI	165	203±79	185/150	—2°, wind, fog, snow
19.XI	180	152±60	187/145	1°
4 XII	195	212±58	180/137	1,5°, cloudy
20.XII	210	224±99	195/147	—6°, windy
5.I	225	177±49	198/147	—7°, cloudy
20.I	240	233±79	185/150	—17°, fog, snow
5.II	255	190±4	180/121	—11°, snow
20.II	270	186±32	178/135	—3°, cloudy

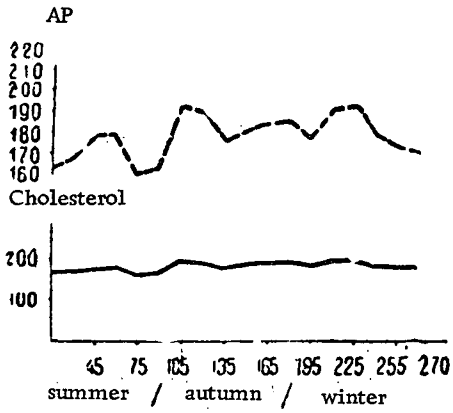

Figure 4. Seasonal Trends in Variation of Cholesterol and Arterial Pressure in Dogs with Hypertonia under the Conditions of the Mountain Climate (2150 m).

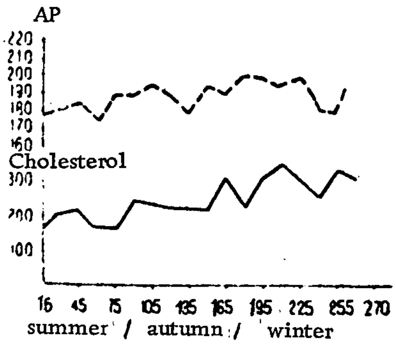

Figure 5. Seasonal Trends in Variation of Cholesterol and Arterial Pressure in Dogs with Hypertonia and Thyroid Function Suppression under the Conditions of the Mountain Climate.

233 mg-%, while the arterial pressure varied between 178/135 and 189/147 mm Hg.

We found no definite relation between the amount of cholesterol and arterial-pressure level. Concerning the dependence of these indicators on weather conditions, Fig. 4 shows a tendency for arterial pressure to rise during the cold period (-2 to -17°C) in the mountains, but no substantial displacements of the blood cholesterol were observed.

Variations of blood cholesterol level in dogs with hypertonia and thyroid hypofunction under the conditions of the mountain climate. In the dogs of group II, which received methylthiouracyl in the mountains, a tendency to hypercholesteremia emerges even during the first 2.5 months (initial stage of thyroid hypofunction). Cholesterol level varied from 172 to 232 mg-%, and arterial pressure from 178/136-190/142 mm Hg.

Blood cholesterol shows a definite increase in the period from the 90th through the 105th day (265-186 mg-%); it decreases slightly during the next one-and-a-half months (to 238 mg-%). Throughout this period, arterial pressure varied from 180/136 to 196/156 mm Hg. /71

From the 165th day to the end of the observations (late autumn and the winter-spring period), the blood cholesterol levels showed a reliable increase, sometimes to more than double the

TABLE 10. VARIATIONS OF CHOLESTEROL CONTENT WITH ARTERIAL PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA AND THYROID HYPOFUNCTION UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE (2150 m)

Date	Day of observation	Cholesterol content, mg-%		Arterial pressure, mm Hg	Air temperature, atmospheric phenomena
		initial 148 ± 9		initial 180 ± 9	
5.VI	15	172±68,		178/136	21°, rain, fog
20.VI	30	216±86		182/120	16°
5.II	45	232±60		185/142	17°
19.VII	60	185±44		175/132	22°
5.VIII	75	182±30		190/142	16°, rain, fog
19.VIII	90	265±53,	$p<0.05$	190/148	20°
4.IX	105	286±40,	$p<0.001$	196/156	13°
22.IX	120	256±72		190/146	18°, windy
7.X	135	255±85		180/136	16°
23.X	150	238±63		196/154	2°, windy
2.XI	165	333±58,	$p<0.01$	190/152	2°, windy, fog, snow
19.XI	180	255±46,	$p<0.05$	202/162	1°
4.XII	195	320±49,	$p<0.01$	260/157	5°, cloudy
20.XII	210	419±86,	$p<0.01$	195/152	6°, windy
5.I	225	326±73,	$p<0.05$	200/160	7°, cloudy
20.I	240	269±15,	$p<0.001$	182/147	17° fog, snow
5.II	255	372±74,	$p<0.01$	180/142	11° snow
20.II	270	313±35,	$p<0.001$	205/162	3°, cloudy

initial level. The lowest value during this period (on the 180th day) was 255 mg-%, and the highest (on the 210th day) 419 mg-%. On these days, the arterial pressures were also high, varying from 180/142 to 205/162 mm Hg.

The meteorotropic nature of hypertonia with simultaneous thyroid hypofunction under the conditions of the 2150-meter elevation is evident from Fig. 5.

It is interesting that hypercholesteremia occurs on the meteorologically uncomfortable days in winter and spring without any supply of exogenous cholesterol. As we have noted, this observation was not made in the animals with "pure" hypertonia over the entire stay in the mountains. /72

Thus, when thyroid function is suppressed in the mountains (2150 m) in dogs with hypertonia, the hypercholesteremia is more pronounced than in dogs with "pure" hypertonia. /73

Variation of blood cholesterol level in dogs with hypertonia, thyroid hypofunction, and alimentary hypercholesteremia under conditions of the mountain climate. In the initial stage of thyroid hypofunction and experimental hypercholesteremia (15th day), as we

TABLE 11. VARIATIONS OF CHOLESTEROL LEVEL AS A FUNCTION OF ARTERIAL PRESSURE AND WEATHER CONDITIONS IN DOGS WITH HYPERTONIA, THYROID HYPOFUNCTION, AND HYPERLIPEMIA UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE (2150 m)

Date	Day of observation	Cholesterol content, mg-%	Arterial pressure, mm Hg	Air temperature, atmospheric phenomena
		initial 148±9	initial 180/129	
5.VI	15	358±39, $p<0.01$	162/123	21°, fog
20.VI	30	353±19, $p<0.01$	177/139	16°
5.VII	45	520±24, $p<0.001$	183/141	17°, rain
19.VII	60	558±32, $p<0.01$	184/144	22°
5.VIII	75	727±22, $p<0.001$	191/148	16°, fog, rain
19.VIII	90	479±4, $p<0.001$	181/138	20°
4.IX	105	638±11, $p<0.001$	191/147	13°
22.IX	120	595±10, $p<0.01$	181/133	18°, windy
7.X	135	620±9, $p<0.001$	185/150	16°
23.X	150	643±10, $p<0.001$	185/150	2°, windy
2.XI	165	699±5, $p<0.001$	193/153	2°, fog, snow
19.XI	180	1117±100, $p<0.001$	208/161	1°
4.XII	195	856±30, $p<0.001$	196/148	-5°
20.XII	210	1509±11, $p<0.001$	200/144	6°, windy
5.I	225	561±5, $p<0.001$	190/136	6°, cloudy
20.I	240	513±10, $p<0.001$	178/136	17°, fog, snow

see from Table 11, the effect of the exogenous cholesterol is to raise the endogenous cholesterol level more sharply (358 vs. 148 mg-%) than under methylthiouracyl treatment (without administration of cholesterol). In spite of the hypercholesteremia, arterial pressure was down to 162/123 (against the initial 180/129) mm Hg on the 15th day.

The cholesterol level reached 520 mg-% on the 45th day and 727 on the 75th. This was accompanied by an arterial-pressure rise to 191/148 mm Hg. The range of cholesterol level during the summer (the first three months) was from 353 to 727 mg-%, while M.Ya. Shchukina (1965) reports 447-510 mg-% for healthy dogs during the first three months at an elevation of 3200 meters. Some of the animals showed a stronger reaction to the administration of exogenous cholesterol, and its level in the blood increased sharply during the very first months of administration. Thus, the content reached 822 mg-% in the dog Arma on the 75th day, 850 in Rybak, 1030 in Pushinka, and 1056 mg-% in Chernaya. The average cholesterol level during the summer months was 500 mg-%, or 235% of the initial level. /74

During the autumn, the average cholesterol level in the dogs of this group was 719 mg-% (from 595 to 1117 mg-%). Arterial pressure varied from 181/133 to 208/161 mm, showing the greatest /75

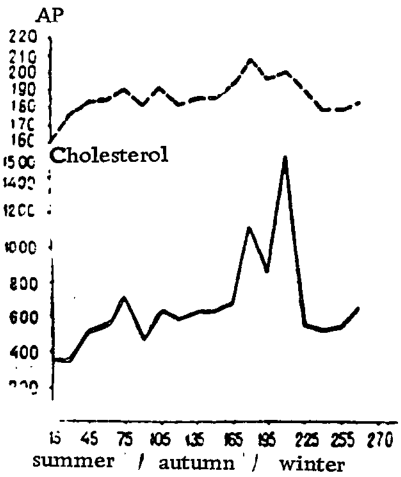

Figure 6. Seasonal Trends in Variation of Cholesterol and Arterial Pressure in Dogs with Hypertonia, Thyroid-Function Suppression, and Alimentary Hypercholesteremia under the Conditions of the Mountain Climate.

increase, to 208/161 mm Hg, on the day of the largest cholesterol-level rise (the 180th), to 1117 mg.

A relatively stable and, on certain days, very high level of hypercholesteremia developed during the winter as the animals received cholesterol and methylthiouracyl (see Fig. 6). The cholesterol content varied from 513 to 1509 mg-% (on the 210th day). The level reached 2378 mg-% in the dog Arma on the 210th day, 2306 in Chernaya, and 1066 in Sil'va.

Thus, in experimental hypertonia "complicated" by thyroid hypofunction and alimentary hypercholesteremia, the blood cholesterol level was higher than in "pure" hypertonia.

Table 12 shows clearly the difference between the blood cholesterol levels of the dogs of the three "mountain" series: it was lowest in the dogs with hypertonia (group I), elevated in those with hypertonia + hypothyroidism (series II), and sharply elevated in those with hypertonia + hypothyroidism + hyperlipemia (series III). /76

Variation of lecithin content and lecithin-cholesterol ratio in dogs with hypertonia, thyroid hypofunction, and alimentary hypercholesteremia under the conditions of the mountain climate. As we noted, much attention is currently being given to blood phospholipid content. A.Ya. Shurygin (1962) observed a decrease in lecithin in hypertonic patients (stages II and III) at an elevation of 1750 m and, conversely, an increase in its level among healthy inhabitants of the mountain locality.

M.Ya. Shchukina (1965) observed an increase in lecithin in dogs being given cholesterol and methylthiouracyl during the first three months of a stay at an elevation of 3200 meters.

Table 13 shows the lecithin variations in the three groups of animals during nine months of observations in the mountains (2150 m).

The lecithin level first rose slightly and then decreased in the group of control dogs with "pure" hypertonia. On the 225th day, its content showed a reliable decrease (to 260 mg-%), but on the 255th and 270th days it had increased to 542-488 against the

TABLE 12. AVERAGE BLOOD CHOLESTEROL LEVELS IN DOGS UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE (2150 m), IN mg-%

Day of observation	Group		
	I (hypertonia)	II (hypertonia + 6-MTU)	III (hypertonia + 6-MTU + Chol.)
15	204±67	172±68	358±39, $p<0{,}05$
30	176±48	216±86	353±19, $p<0{,}05$
45	153±9	232±60, $p<0{,}01$	520±24 $p<0{,}001$
60	149±32	185±44	558±32, $p<0{,}001$
75	159±33	182±30	727±22, $p<0{,}001$
90	188±48	265±53	479±4, $p<0{,}001$
105	181±60	286±40	638±11, $p<0{,}01$
120	172±41	256±72	595±10, $p<0.01$
135	157±38	255±85	620±9, $p<0{,}001$
150	156±50	238±63	643±10, $p<0{,}001$
165	203±79	333±50	699± 5 $p<0{,}001$
180	152±60	255±46	1117±100, $p<0{,}001$
195	212±58	320±49	856±30, $p<0{,}001$
210	224±99	419±86	1509±11, $p<0{,}001$
225	177±49	326±73	561±5, $p<0{,}001$
240	233±79	269±15	513±10, $p<0{,}001$
255	190±4	372±74, $p<0{,}05$	555±80, $p<0{,}01$
270	186±32	313±35, $p<0{,}01$	676±10, $p<0{,}001$

initial 354 mg-%. Over the entire time of the observations, lecithin content varied from 260 to 542 mg-%.

In the dogs with hypertonia and thyroid hypofunction, lecithin level rose starting on the 15th day (492 vs. 354 mg-%), although the rise did not become statistically definite until the 30th day (553 mg-%). During the next one-and-a-half months, its content decreased slightly, reaching the initial level. Beginning on the 90th day and almost until the end of the observations, there was a reliable increase in the amount of lecithin. The 120-th, 150th, and 225th days are exceptions. On certain days, the lecithin content almost doubled (to 613 against the initial 354 mg-%).

The amount of lecithin had also increased on the 15th day in the dogs with hypertonia + hypothyroidism + hypercholesteremia (to nearly double: 679 vs. 354 mg-%). However, pronounced and statistically reliable hyperlecithinemia was observed only starting on the 55th day; it persisted until the 355th.

During the first three months, the lecithin level in this group of dogs varied from 624 to 1287 mg-%, while, according to M.Ya. Shchukina (1965), it varied from 740 to 847 mg-% in dogs that were normotonic but hypothyroid and hypercholesteremic under the conditions of a 3200-meter elevation. /77

Subsequently, the lecithin content also increases with increasing cholesterol level. The highest content was recorded on

TABLE 13. VARIATIONS OF LECITHIN CONTENT IN DOGS (INITIAL CONTENT 354±27) UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE, IN mg-%

Day of observation	Group		
	I (hypertonia)	II (hypertonia + 6-MTU)	III (hypertonia + 6-MTU + Chol.)
15	469±124	492±38	679±226
30	501±3	533±35, p<0,001	624±201
45	364±32	406±21	990±190, p<0,01
60	324±38	489±88	1061±61, p<0,001
75	290±33	438±46	1287±23, p<0,001
90	402±36	480±25, p<0,001	697±20, p<0,001
105	394±28	440±25, p<0,05	948±66, p<0,001
120	316±32	424±51	1037±62, p<0,001
135	309±28	516±38, p<0,01	643±38, p<0,001
150	378±26	414±53	658±44, p<0,001
165	396±30	589±60, p<0,01	684±37, p<0,001
180	409±32	613±51, p<0,001	179±82, p<0,001
195	422±28	573±77, p<0,02	1666±85, p<0,001
210	377±35	595±88, p<0,05	1905±114, p<0,001
225	260±13, p<0,01	319±65	983±36, p<0,001
240	527±103	536±79, p=0,005	926±27, p<0,001
255	542±42, p=0,02	605±90, p=0,05	962±54, p<0,001
270	488±40, p<0,02	575±90, p<0,005	571±120

the 210th day (1905 mg-%). This is more than five times the initial level. While the lecithin level also decreased (for example, to 571 mg-% on the 270th day), it was still higher than the initial level.

It is known that the absolute phospholipid value characterizes the state of lipid metabolism only partially. It is important to consider the coefficient reflecting the proportions of phospholipids and cholesterol. A low lecithin-cholesterol ratio indicates the predominance of cholesterol over phospholipids and the possibility that the former may be deposited (M.V. Bavina, 1951; Yu.T. Pushkar', 1953; Morrison, 1952).

Some clinicians do not attach great importance to this indicator, since it is found to be low in a small percentage of atherosclerotics (B.V. Il'inskiy, 1954; P.Ye. Lukomskiy, 1960, and others).

We felt it worthwhile to investigate the variations of the lecithin-cholesterol ratio with the purpose of establishing the influence of the mountain climate on the course of experimental hypertonia and the development of the atherosclerotic process with hypertonia as a background. /78

In the dogs with "pure" hypertonia, the lecithin-cholesterol ratio varied in the initial range (Table 14) – from 2.1 to 3.2 – during the first two months. On the 75th day, it showed a reliable decrease (to 1.83 against the initial 2.81). However, this

TABLE 14. VARIATIONS OF LECITHIN-CHOLESTEROL RATIO (INITIAL VALUE 2.81±0.3) IN DOGS UNDER THE CONDITIONS OF THE HIGH MOUNTAINS (2150 m)

Day of observation	Group		
	I (hypertonia)	II (hypertonia + 6-MTU)	III (hypertonia + 6-MTU + Chol.)
15	2,29±0,14	2,58±0,5	1,98±0,3
30	3,20±0,48	2,65±0,25	2,06±0,28
45	2,35±0,1	1,81±0,18. $p=0,01$	1,9 ±0,07, $p<0,01$
60	2,10±0,17	2,59±0,16	1,9 ±0,15, $p<0,01$
75	1,83±0,19, $p<0,02$	2,58±0,3	1,82±0,16, $p<0,01$
90	2,19±0,11	1,82±0,1, $p<0,01$	1,48±0,07, $p<0,001$
105	2,39±0,19	1,58±0,1, $p<0,02$	1,5 ±0,16, $p<0,001$
120	1,85±0,14, $p<0,02$	1,66±0,25, $p<0,02$	1,8 ±0,02; $p<0,01$
135	1,99±0,33	1,08±0,4	1,02±0,1, $p<0,001$
165	2,00±0,14, $p<0,05$	1,86±0,21, $p<0,02$	1,00±0,11, $p<0,001$
180	2,85±0,3	2,24±0,37	1,50±0,16, $p<0,002$
195	2,04±0,2, $p<0,05$	2,03±0,16, $p<0,05$	1,93±0,2, $p<0,05$
210	1,84±0,7, $p<0,02$	1,52±0,16, $p<0,01$	1,21±0,12, $p<0,001$
225	1,45±0,17, $p<0,002$	0,99±0,06, $p<0,001$	1,8 ±0,07, $p<0,01$
240	2,25±0,18	2,35±0,43	1,83±0,07, $p<0,01$
255	2,83±0,25	1,80±0,4, $p<0,05$	1,72±0,1, $p<0,01$
270	2,59±0,22	1,97±0,38	1,65±0,09, $p<0,01$

decrease was not stable, and the ratio later decreased and rose to the initial value by turns. We observed a distinct depression of this ratio on the 120th, 165th, 195th, 210th, and 225th days of the stay in the mountains. On these days, it varies from 1.45 to 2.04, i.e., within the physiologically normal range of 1.3-2 (L.P. Bondar', cited from I.D. Mansurova and M.Kh. Khodi-zade, 1960).

The lecithin-cholesterol ratio is considered low when its value is smaller than unity.

The decrease in this coefficient in dogs with "pure" hypertonia is evidently due to the rise in the cholesterol level, which /79 is not accompanied by substantial changes in the blood lecithin level under the conditions of the mountain climate.

A similar pattern was observed in the group II dogs (hypertonia + 6-methylthiouracyl). During the period between the 15th and 75th days, the lecithin-cholesterol coefficient was reliably down only on the 45th day (1.81 vs. the initial 2.81). On the other days, except for the 135th, 150th, 180th, 240th, and 270th, it varied from 0.99 to 2.03.

In the group III animals (hypertonia + 6-MTU + Chol.), this coefficient remained in the normal range for the first month and then showed a statistically reliable decrease. Its minimum was 1 and its maximum 1.93.

TABLE 15. BLOOD CHOLESTEROL CONTENT IN DOGS IN "URBAN" AND "MOUNTAIN" EXPERIMENTAL SERIES, IN mg-% /81

Day of observation	Group					
	I (hypertonia)		II (hypertonia + 6-MTU)		III (hypertonia + 6-MTU + Chol.)	
	City	Mountains	City	Mountains	City	Mountains
Initial value	134±4	148±9	134±4	148±9	134±4	148±9
15	105±15	204±67	121±33	172±68	269±30	358±39, $p<0.05$
30	171±19	176±48	209±35	216±86	376±49	353±19
45	186±21	153± 9	239±95	232±60	589±32	520±24
60	182±15	149±32	215±22	185±44	371±52	558±32, $p<0.05$
75	176±24	159±33	216±24	182±30	412±50	727±22, $p<0.001$
90	115±21	188±48	143±14	265±53, $p<0.05$	442±26	479±4
105	147±27	181±60	165±33	286±40, $p<0.05$	376±34	638±11, $p<0.001$
120	141±15	172±41	149±29	256±72, $p<0.05$	378±22	595±10, $p<0.001$
135	151±7	167±38	198±46	255±85	487±51	620±9 $p<0.05$
150	143±26	166±50	167±45	238±63	544+76	643±10, $p<0.02$
165	192±31	203±79	187±19	333±50, $p<0.05$	926±118	699±5, $p<0.05$
180	218±48	152±60	293±37	255±46	704±56	1117±100, $p<0.01$
195	143±86	212±58	263±57	320±49	810±86	856±30
210	167±15	224±99	309±32	419±86	791±91	1509±11, $p<0.01$
225	165±90	177±49	291±33	326±73	1072±398	561±5, $p<0.05$
240	189±65	233±79	208±61	269±15	372±144	513±10
255	181±46	190±4	236±21	372±74, $p<0.01$	482±102	555±80
270	156±14	186±32	232±9	313±35, $p<0.05$	585±90	676±10

Thus, the lecithin-cholesterol ratio shows a statistically reliable decrease in hypertonia accompanied under alpine conditions by thyroid hypofunction and hypercholesteremia.

Above we have described the nature of the lipid variations in the blood of dogs of the "lowland" and "mountain" experimental series. In the analysis, comparisons were drawn only between the separate groups of "lowland" and "mountain" animals. However, /80 only comparison of the results of "lowland" and "mountain" series yields an answer to the question as to where (in the mountains or in the lowlands) conditions are more favorable for the appearance of atherosclerosis against the background of the hemodynamic factor, i.e., hypertonia.

Table 15 presents comparative data on the variations of blood cholesterol level in three groups of animals kept for extended periods under "lowland" (Frunze) and mountain (2150 m) conditions.

As we see from Table 15 and Fig. 7, there are no sharp differences in cholesterol level among the dogs with "pure" hypertonia, although there is a tendency for it to increase in the mountains: in 18 examinations (from the 15th through the 270th day), the cholesterol level was higher here than in the city in 14 cases, varying from 149 to 233 mg-% as against 105-218 in the city.

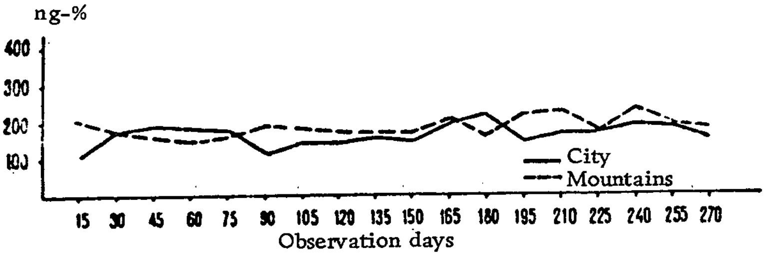

Figure 7. Variations of Cholesterol in Dogs with Hypertonia Under Urban and Mountain Conditions.

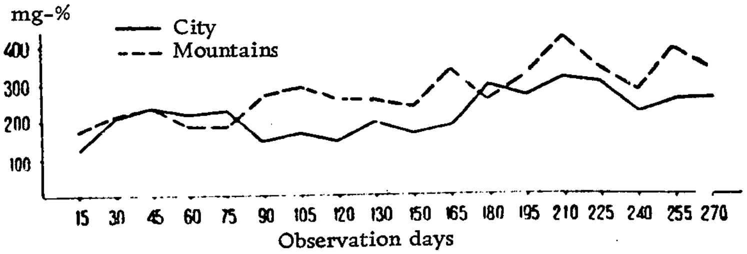

Figure 8. Variations of Cholesterol in Dogs with Hypertonia and Thyroid-Hypofunction Under Urban and Mountain Conditions.

Thus, despite the comparatively favorable course of hypertonia in the mountains, hypercholesteremia is still more pronounced here than under "lowland" conditions.

No differences in cholesterol content are observed in the hypertonic dogs with thyroid hypofunction (series II) under urban and mountain conditions during the first 2.5 months. From the third month, however, hypercholesteremia was more pronounced in the "mountain" animals (see Table 15 and Fig. 8). The cholesterol content was definitely high on the 90th, 105th, 120th, 165th, 255th, and 270th days in the mountains, although the increase was not reliable the rest of the time. In 18 determinations of cholesterol that were made both in the city and in the mountains in the span between the 15th and 270th days, the level was higher in 15 of the "mountain" dogs than in the "lowland" dogs. While hypercholesteremia seldom prevailed reliably among the dogs with "pure" hypertonia, in the mountains, it was more pronounced and /82 of longer duration when hypertonia was combined with hypothyroidism. While the cholesterol level varied from 143 to 309 mg-% in the "urban" dogs with hypertonia and hypothyroidism (compared to 105-218 for the "urban" control animals), it was 172-419 for the "mountain" animals (vs. 149-233 for the "mountain" controls).

From this we may conclude that the combination of hypertonia with thyroid hypofunction produces a more pronounced and stable hypercholesteremia during a nine-month stay in the mountains (2150 m) than it does in the "lowlands."

Let us now consider the variations of cholesterol level when the pathological states are combined (hypertonia, hypothyroidism, hypercholesteremia, i.e., the atherosclerotic complex) in the mountains and on the "lowlands" (Table 15 and Fig. 9). From the second month of the cholesterol-methylthiouracyl regime, we observe reliable prevalence of hypercholesteremia in the "mountain" as compared with the "urban" dogs: in 18 determinations, hypercholesteremia was found in 15, and the high cholesterol level was statistically reliable in 11 out of these 15 cases. While the cholesterol content of the blood varied from 269 to 1072 mg-% in the "urban" dogs of this series (vs. 143-309 in the "urban" dogs with hypertonia and hypothyroidism), it was 358-1117 among the "mountain" dogs (against 172-419 for the "mountain" dogs with hypertonia and hypothyroidism).

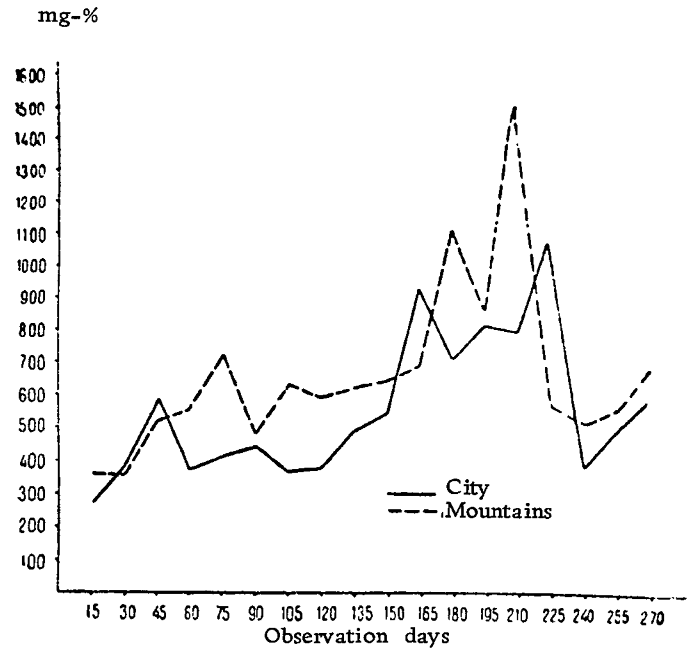

Figure 9. Variations of Cholesterol in Dogs with Hypertonia, Thyroid Suppression, and Hypercholesteremia under Urban and Mountain Conditions.

Thus, during a nine-month stay in the mountains (2150 m), the combination of hypertonia with hypothyroidism and alimentary hypercholesteremia has a more pronounced hypercholesteremic effect than it does in the "lowlands."

Although there is no doubt as to the importance of the cholesterol factor in the pathogenesis of atherosclerosis, hypercholesteremia is not always a reliable indicator of the atherosclerotic process (A.L. Myasnikov, 1924, 1965; N.A. Sokolov, 1925). /83

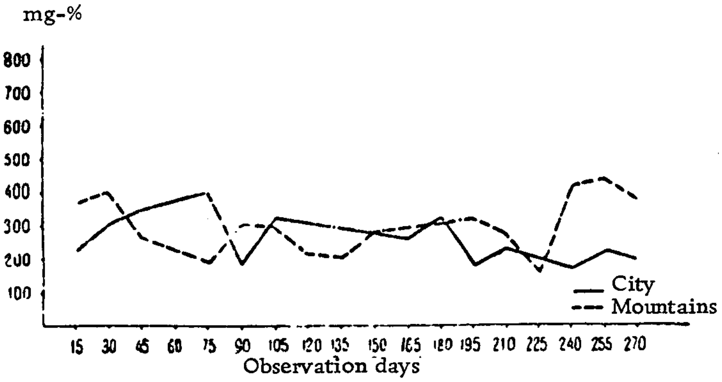

Figure 10. Variations of Lecithin in Dogs with Hypertonia under Urban and Mountain Conditions.

"It must be assumed," wrote N.N. Anichkov (1937), "that the deposition of cholesterol in the arterial walls depends not only on a disturbance to cholesterol metabolism, but also on a whole series of other phenomena; these include, for example, the proportions of the individual lipids. Thus, the content of lecithin, in addition to that of cholesterol, is an important factor in the development of atherosclerosis. An increase in the blood phospholipid content tends to keep the cholesterol in the dissolved state and is appraised as a protective reaction of the organism to the reaction that increases cholesterol."

Lecithin content declines slightly from the 45th through the 135th day in the mountains in the animals with "pure" hypertonia (Table 14), but this decrease is not stable and the level is slightly increased during the second phase of the observations (from the 135th through the 270th day). This increase was statistically reliable during the last one-and-a-half months (see Fig. 10). Lecithin varied from 275 to 507 mg-% on the "lowlands," and from 260 to 542 in the mountains. Among 18 determinations, nine showed an increase in lecithin level in the "mountain" dogs with hypertonia as compared with the "urban" animals. /84

We see from Table 16 and Fig. 11 that there was a statistically significant difference between the lecithin levels of the dogs with hypertonia and hypothyroidism from the fifth month of their

TABLE 16. BLOOD LECITHIN CONTENTS OF DOGS IN "URBAN" AND "MOUNTAIN" EXPERIMENTAL SERIES, IN mg-% /85

Day of observation	Group					
	I (hypertonia)		II (hypertonia + 6-MTU)		III (hypertonia + 6-MTU + Chol.)	
	City	Mountains	City	Mountains	City	Mountains
Initial value	364±23	354±27	364±23	354±27	364±23	354±27
1	327±65	469±124	388±92	492±38	614±190	679±226
30	410±11	501±3, p<0,001	505±66	555±35	726±74	624±201
45	451±59	364±32	477±53	406±21	787±84	990±190
60	479±35	324±38, p<0,02	533±82	489±88	730±76	1061±16, p<0,001
75	507±41	290±33, p<0,01	423±28	438±46	712±59	1287±23, p<0,001
90	280±48	402±36	493±25	480±25	804±43	697±20
105	427±55	394±28	357±110	440±25	512±49	948±66, p<0,001
120	413±13	316±32	497±55	424±51	729±71	1037±62, p<0,001
135	398±25	309±28	508±51	516±38	868±83	643±38
150	380±52	378±26	395±82	414±53	950±96	658±44, p<0,02
165	363±51	396±30	360±27	589±60	807±100	684±37
180	425±37	409±32	512±62	613±51	642±120	1799±82, p<0,001
195	285±55	422±28, p<0,05	500±30	573±77	678±210	1666±85, p<0,001
210	335±56	377±35	487±31	595±88	499±60	1905±114, p<0,001
225	295±42	260±13	510±50	319±65	700±103	983±36, p<0,05
240	275±44	527±103, p<0,05	265±28	536±79, p<0,002	351±87	926±27, p<0,01
255	325±25	542±42, p<0,02	330±52	605±90, p<0,02	369±34	962±54, p<0,01
270	295±36	488±40, p<0,02	343±51	575±90, p<0,05	552±36	571±112

stay in the mountains as compared with the equivalent "urban" dogs. Of the 18 determinations, the lecithin levels were higher in the "mountain" dogs as compared with the "lowland" dogs in 13 cases; admittedly, only four cases of hyperlecithinemia were statistically reliable out of the 13. While the lecithin level varied from 357 to 533 mg-% in the "urban" dogs with hypertonia and hypothrodism (compared to 280-507 for the "urban" controls), it was 319-605 in the "mountain" animals (vs. 290-527 for the "mountain" controls).

Thus, a more pronounced hyperlecithinemia was observed under the conditions of the high mountains (2150 m) than on the "lowlands" in the animals with hypertonia and hypertonia combined with /86 thyroid hypofunction, especially during the later stages (seventh to eleventh month).

We see from Table 16 and Fig. 12 that the lecithin level was substantially higher under both urban and mountain conditions in the dogs with hypertonia and such attendant pathological states as hypothyroidism and hypercholesteremia than it was in the animals of the other two groups. But the hyperlecithinemia was more pronounced and of longer duration in the "mountain" experiments: firstly, a statistical difference between the "lowland" and "mountain" data appears very early from the second month); secondly, the hyperlecithinemia was more pronounced under the conditions of the mountain climate (2150 m) than in the city in 13 out of 18 determinations; thirdly, while the lecithin level in "lowland"

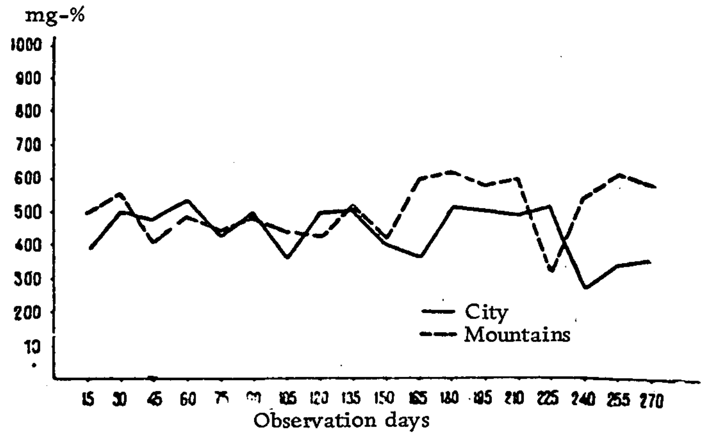

Figure 11. Variations of Lecithin in Dogs with Hypertonia and Thyroid-Function Suppression under Urban and Mountain Conditions.

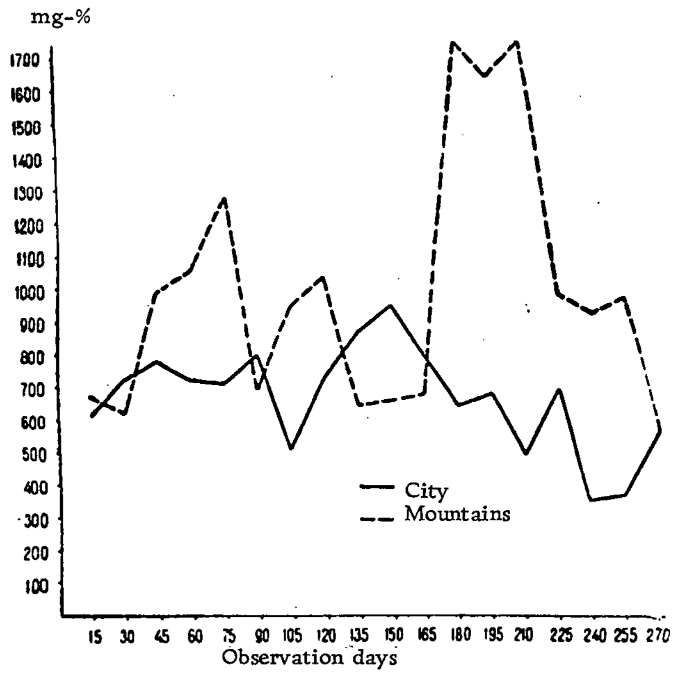

Figure 12. Lecithin Variations in Dogs with Hypertonia and Cholesterol-Methylthiouracyl Treatment under Urban and Mountain Conditions.

dogs of this series varied from 351 to 950 mg-% (against 357-533 for "urban" animals with hypertonia and hypothyroidism), it was 571-1905 for the "mountain" animals (against 319-605 for "mountain" dogs with hypertonia and hypothyroidism).

TABLE 17. VARIATION OF LECITHIN-CHOLESTEROL COEFFICIENT IN DOGS UNDER "LOWLAND" AND MOUNTAIN (2150 m) CONDITIONS /88

Day of observation	Group					
	I (hypertonia)		II (hypertonia + 6-MTU)		III (hypertonia + 6-MTU + Chol.)	
	City	Mountains	City	Mountains	City	Mountains
Initial value	2,88±0,3	2,81±0,3	2,88±0,3	2,81±0,3	2,88±0,3	2,81±0,3
15	3,05±0,49	2,29±0,14	3,1 ±0,57	2,58±0,5	2,37±0,24	1,98±0,3
30	2,39±0,09	3,20±0,48	2,42±0,24	2,65±0,25	1,99±0,14	1,06±0,28
45	2,42±0,12	2,35±0,13	3,17±0,9	1,81±0,16	1,85±0,15	1,9 ±0,07
60	2,66±0,13	2,10±0,17	2,48±0,57	2,58±0,3	1,89±0,24	1,9 ±0,15
75	2,95±0,32	1,83±0,19, $p<0{,}02$	1,96±0,18	1,82±0,1	1,77±0,13	1,82±0,16
90	2,66±0,82	2,19±0,11	2,53±095	1,58±0,1	1,83±0,1	1,48±0,07, $p<0{,}02$
105	2,99±0,4	2,39±0,19	2,78±0,95	1,66±0,25	1,76±0,37	1,5 ±0,16
120	2,97±0,27	1,85±0,14, $p<0{,}01$	3,23±0,63	2,08±0,4	1,94±0,21	1,8 ±0,13
135	2,63±0,08	1,99±0,33	2,65±0,16	2,02±0,77	1,78±0,13	1,02±0,1, $p<0{,}001$
150	2,60±0,17	2,46±0,13	3,03±0,71	1,86±0,21	1,8 ±0,19	1,07±0,1, $p<0{,}001$
165	1,91±0,05	2,00±0,14	1,65±0,17	2,24±0,37	1,44±0,44	1,20±0,10
180	1,99±0,27	2,85±0,3, $p<0{,}02$	2,32±0,45	2,03±0,16	1,2 ±0,27	1,50±0,16
195	2,00±0,47	2,04±0,2	2,09±0,49	1,52±0,16	1,08±1,18	1,93±0,2, $p<0{,}01$
210	2,95±0,03	1,84±0,17, $p<0{,}001$	1,48±0,06	1,52±0,16	1,2 ±0,27	1,21±0,12
225	1,01±0,05	1,45±0,17, $p<0{,}02$	1,72±0,3	0,99±0,06, $p<0{,}001$	0,05±0,11	1,8 ±0,07, $p<0{,}001$
240	2,46±0,5	2,25±0,18	1,2 ±0,33	2,35±0,43, $p<0{,}05$	0,94±0,24	1,83±0,07, $p<0{,}01$
255	2,81±0,6	2,83±0,25	1,43±0,64	1,80±0,4	0,77±0,17	1,72±0,14, $p<0{,}01$
270	2,9 ±0,03	2,59±0,22	1,57±0,3	1,97±0,38	0,99±0,12	1,65±0.09, $p<0{,}01$

From this we may conclude that the combination of hypertonia with a hypofunctional state of the thyroid gland and alimentary hypercholesteremia during a prolonged stay in the mountains causes an earlier (from the first month) onset of hyperlecithinemia, which becomes most pronounced (up to 1900 mg-% against an initial 364) at a later stage (months 7-11) than the hypertonia, hypothyroidism, /87 and hypercholesteremia (months 5-9). It may be that the lecithin reaction is the basis of resistance to atherosclerosis.

Let us examine the results on the variations of the lecithin-cholesterol ratio from these aspects.

The lecithin-cholesterol ratio undergoes no changes in either the "lowland" or "mountain" animals of group I (Table 17). True, its value is significantly lower in the mountains on some days, but it does not leave the physiologically normal range.

The same can be said concerning the group II animals, which were given methylthiouracyl: the lecithin-cholesterol ratio does not drop below one in either the city or the mountains; it very /89 seldom approaches the lower boundary of the normal range.

In the group III dogs, this coefficient varies in the same range on the "lowlands" and at elevation from the 15th through the 165th day, but on certain days it is markedly lower in the mountains (down to 1.02-1.07); in the mountains, there is a statistically reliable increase during the next 3.5 months (1.21-1.93),

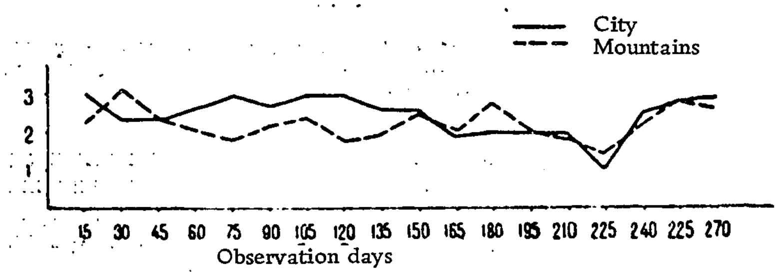

Figure 13. Lecithin-Cholesterol Ratio in Dogs with Hypertonia under Urban and Mountain Conditions.

while the ratio is down in the city during this period (0.5-1.2).

The lecithin-cholesterol coefficient decreases in cholesterol atherosclerosis, and the extent of lipid accumulation in the aorta depends to a substantial degree on this indicator (M.V. Bavina, 1951: Kellner, Correl, Ladd, 1951). Thus, the increase in the lecithin-cholesterol ratio in the hypertonic dogs that were given cholesterol and methylthiouracyl in the mountains – especially during the latter phase of this treatment (225th to 270th day) – should be regarded as a helpful effect. Obviously, despite the pronounced hypercholesteremia in the mountains, the hyperlecithinemia and the high lecithin-cholesterol coefficient form a basis for prevention of atherosclerosis. This is clearly demonstrated by Figs. 13, 14, and 15.

Hypercholesteremia was more pronounced in the hypertonic dogs kept for the long period in the mountains (2150 m) than under the urban, "lowland" conditions, in spite of its mild course (there were no abrupt pressor shifts or "crises"). In the dogs with hypertonia and hypothyroidism that were also kept under the conditions of the mountain climate, hypercholesteremia was still more pronounced (419 mg-%) than in the dogs with hypertonia and hypothyroidism on the "lowlands" (309 mg-%).

The combination of hypertonia with hypothyroidism and alimentary hypercholesteremia produces the most pronounced hypercholesteremia (358-1117 mg-%) during the long stay of the animals in the mountains, and the cholesterol level is lower under "lowland" conditions (269-1072 mg-%). /90

Admittedly, the cholesterol-methylthiouracyl regime produces, in itself, a rather high degree of hypercholesteremia in the hypertonic animals under urban conditions as compared with "pure" hypertonia and methylthiouracyl suppression of thyroid function without introduction of exogenous cholesterol.

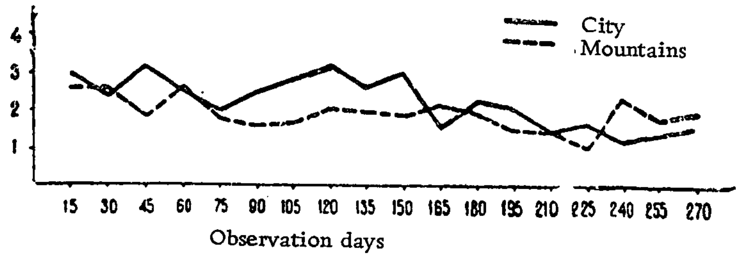

Figure 14. Lecithin-Cholesterol Ratio in Dogs with Hypertonia and Thyroid-Function Suppression under Urban and Mountain Conditions.

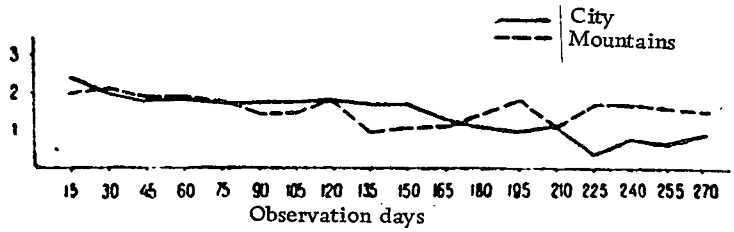

Figure 15. Cholesterol-Lecithin Ratio in Dogs with Hypertonia, Suppression of Thyroid Function, and Cholesterol Feeding under Urban and Mountain Conditions.

During the last month of their stay in the mountains, the lecithin content in the blood of the hypertonic dogs is higher than that in the hypertonic "lowland" animals. A more pronounced degree of hyperlecithinemia appears at 2150 meters than on the "lowlands" when hypertonia is combined with thyroid hypofunction, especially in the later stages of the hypertonia (7th to 11th month) and hypothyroidism (5th to 9th month). /91

Hypertonia accompanied by thyroid hypofunction and alimentary hypercholesteremia under the conditions of the mountain climate gives rise to an earlier (from the first month) onset of hyperlecithinemia, which becomes most pronounced during the later phases (5th to 9th month) of the cholesterol-methylthiouracyl regime. True, the hyperlecithinemic effect is also characteristic for hypertonic animals subject to the cholesterol and methylthiouracyl regime under "lowland" conditions.

The lecithin-cholesterol ratio undergoes no substantial changes in the hypertonic dogs with and without hypothyroidism, either in the mountains or on the "lowlands." However, in hypertonic animals given cholesterol and methylthiouracyl in the mountains, it shows a significant increase at the 7th to 9th months; this should b regarded as a highly important phenomenon from the standpoint of preventing atherosclerosis.

Chapter V

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PATHOMORPHOLOGICAL CHANGES IN THE HEART AND AORTA IN ATHEROSCLEROSIS MODELLED AGAINST A BACKGROUND OF HYPERTONIA UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE*

Study of the influence of the alpine factors on lipid metabolism (cholesterol, lecithin, lecithin-cholesterol ratio) when atherosclerosis is induced against a background of renovascular hypertonia has shown that there are no substantial differences in the cholesterol levels of animals with "pure" hypertonia under "lowland" conditions as compared to healthy animals. However, the cholesterol levels were higher in the hypertonic animals in the mountains than they were in the city. The greatest increases in cholesterol level occur in the winter and early spring.

No consistent variations in cholesterol content were observed during the first 2.5 months in hypertonic animals with hypothyroidism under either "lowland" or alpine conditions. However, a more pronounced hypercholesteremia is observed beginning with the third month in the "mountain" dogs.

Thus, the combination of hypertonia with a hypofunctioning state of the thyroid gland gives rise to a more distinct, stable hypercholesteremia during a long (nine-month) stay in the mountains (2150 m) than it does in the "lowlands."

In animals with the combined pathological state (hypertonia + hypothyroidism + hypercholesteremia), the latter is found to prevail in the "mountain" dogs as compared with the "lowland" dogs as soon as from the second month of the regime.

But what morphological confirmation do we have for the hypofunctional state of the thyroid gland?

The follicles were of average size and uniform diameter in the animals with "pure" hypertonia (both "mountain" and "lowland"). Some of them were elongated and filled with a deep-staining colloidal fluid. A few resorbed vacuoles are observed in others, and the epithelium is distended and congested. The interstitial tissue has expanded in some cases and appears edematous. However, the gland is morphologically rather inactive. /93

The thyroid gland of the group III animals (hypertonia + cholesterol-6-methylthiouracyl regime) had undergone approximately

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*The morphological analysis was carried out by Prof. B.F. Malyshev (now deceased), with the assistance of R.I. Kulakova, S.K. Makova, and K.A. Abdyddayev.

the same changes in the mountains and on the "lowlands." Thus, the follicles vary in size, with extremely hypertrophied formations encountered against a background of average sizes. Their cavities are often filled with a thick colloid that stains deeply without resorbed vacuoles (Fig. 16). They are sometimes filled with a liquid colloid. The epithelial cells lining the walls are flat in places and in some cases cubic in shape. Proliferation is noted in many follicles, with formation of papillae that grow into the cavity of the follicle. Sanderson's bodies have formed in some cases. The interfollicular cells have hypertrophied and formed microfollicles filled with colloidal fluid.

Figure 16. Changes in Thyroid Gland After 6-Methylthiouracyl Treatment. Magnification 2 × 40, hematoxylin + eosin.

Thus, prolonged exogenous administration of 6-methylthiouracyl under both "lowland" and alpine conditions results in thyroid hypofunction in dogs with hypertonia. /94

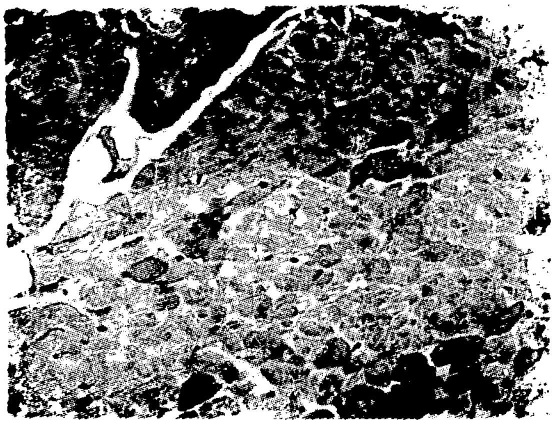

Figure 17. Plasmatic permeation of a precapillary artery. Magnification 2 × 40, hematoxylin + eosin.

Figure 18. Heart. Petrification of precapillary artery. Magnification 2 × 40, hematoxylin + eosin.

The heart-muscle fibers of the "mountain" dogs with hypertonia + hypothyroidism + hypercholesteremia are slightly

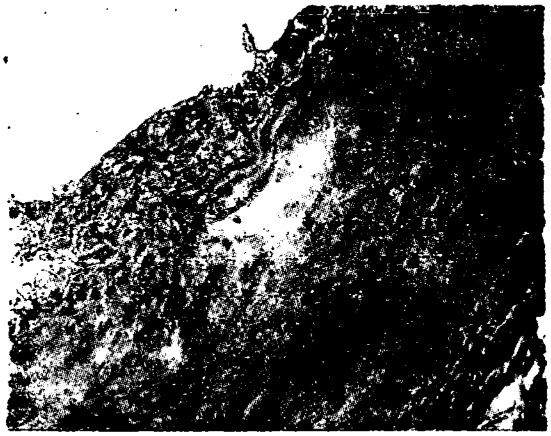

Figure 19. Heart. Small fibrous plaque in coronary artery. Magnification 2 × 40, fuchsilin.

Figure 20. Heart. Moderate xanthomantosis at the branch point of a small coronary artery. Magnification 2 × 40, van Gieson's stain.

hypertrophied; turbid swellings are found in the sarcoplasm of some fibers, and in some places the muscle fibers have lost their /95 transverse striations. The connective tissue is edematous, and plasmatic permeation is observed (Fig. 17). Heavy vascular edema, petrification, and sclerosis are sometimes observed (Fig. 18).

Plaques are observed from time to time in the coronary artery (Fig. 19), and signs of xanthomatosis appear (Fig. 20). Figure 21 shows adiposis of the middle coat of a coronary artery. /96 The intercellular substance is edematous and shows mucoid swelling.

There was a similar pattern of changes in the heart wall in /97 the "urban" dogs (hypertonia + hypothyroidism + hypercholesteremia); as in the "mountain" animals, the walls of small arteries were sclerotic (Fig. 22). Clusters of xanthoma cells are found in the middle coat of the coronary arteries (Figs. 23 and 24).

The same morphological changes were observed in the heart /98 walls of animals of the first (hypertonia) and second (hypertonia + hypothyroidism) series as in the animals of the third series (hypertonia + hypothyroidism + hypercholesteremia).

Thus, the changes in the hearts of the animals of all three groups present approximately the same morphological pattern, which is characteristic for the most part of hypertonia.

Let us now consider the morphological description of the wall of the aorta; this is important for evaluation of the atherosclerotic process in the animal experiment.

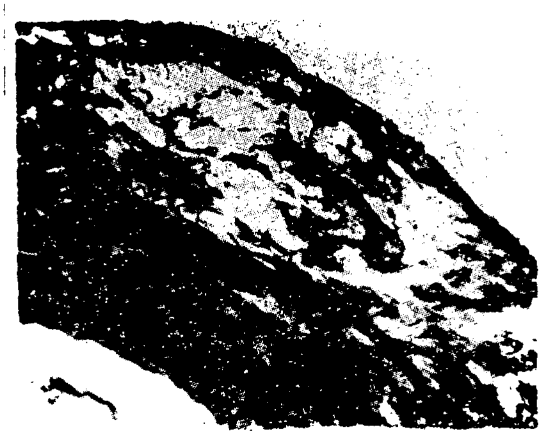

Figure 21. Moderate adiposis of the middle coat of a coronary artery. Magnification 2 × 10, fuchsilin.

Figure 22. Heart. Sclerosis of a small artery. Magnification 2 × 40, van Gieson's stain.

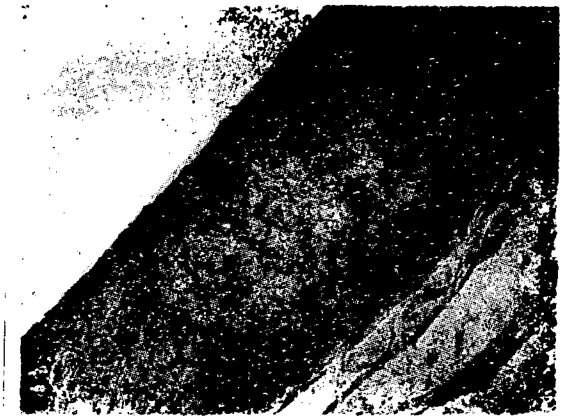

Figure 23. Heart. Hypertrophy of xanthomatous cells in middle coat of left coronary artery. Magnification 2 × 40, hematoxylin + eosin.

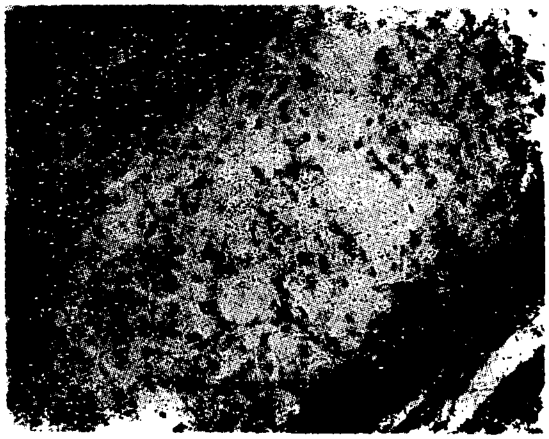

Figure 24. Heart. Xanthomatosis of coronary artery. Magnification 2 × 40, hematoxylin + eosin.

In the hypertonic "urban" dogs given cholesterol and 6-methylthiouracyl, the walls of the aorta show uneven changes. Changes are observed for the most part in the middle coat. Here the bundles of smooth-muscle cells have been pushed apart by the intercellular matter, which is in a state of mucoid edema (Fig. 25). In spots, the muscle cells are defibrillated and atrophied and have been replaced by loose connective tissue.

Figure 25. Aorta. Mucoid swelling in middle coat. Magnification 2 × 20. Sudan III.

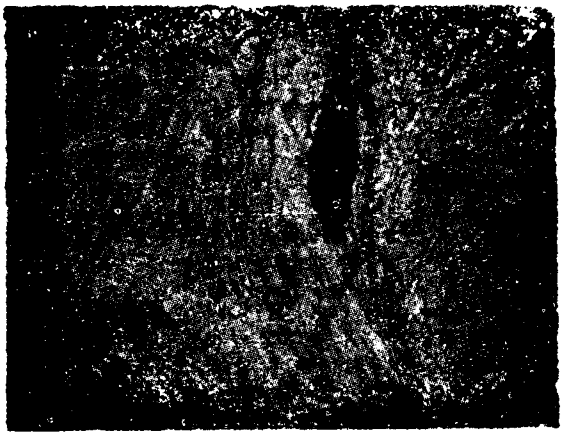

Figure 26. Aorta. Perivascular fibrosis. Magnification 2 × 40. Sudan III.

Figure 27. Aorta. Fibrous plaque in intima. Magnification 2 × 40, hematoxylin + eosin.

In certain cases, xanthoma cells are observed in the walls of the vasa vasorum; they stain orange with Sudan III and, when in the lumina of these vessels, contain large amounts of the dye. Perivascular fibrous hypertrophy sometimes occurs around such vessels, or calcium is deposited in their modified walls (Fig. 26).

Only in one case (in the dog- /99
Zhuchka) was the intima significantly thickened (Fig. 27). The thickenings are disposed in the form of fibrous placques without vacuoles of fat. The middle coat is thickened under the plaque. The intima is also thickened where there are no plaques, but more uniformly. Swelling of the intercellular substance with the char- /100
acteristic mucoid edema is observed in the middle coat.

The morphological picture of the aorta in the "mountain" dogs is similar to that of the "urban" animals. Nonuniform thickening of the intima is again observed. Muscle fibers have been pushed apart by intercellular substance with mucoid edema (Figs. 28 and 29). Small amounts of deposited lipids were observed in /101
three dogs in the interstitial tissue of the middle coat of the

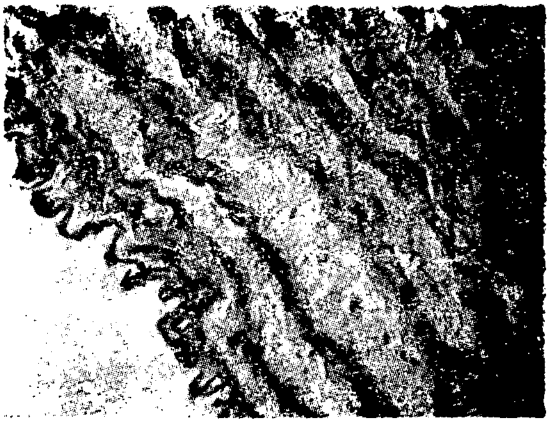

Figure 28. Aorta. Mucoid swelling in middle coat. Magnification 2 × 40, fuchsilin.

Figure 29. Aorta. Mucoid swelling in middle coat. Magnification 2 × 40, van Gieson's stain.

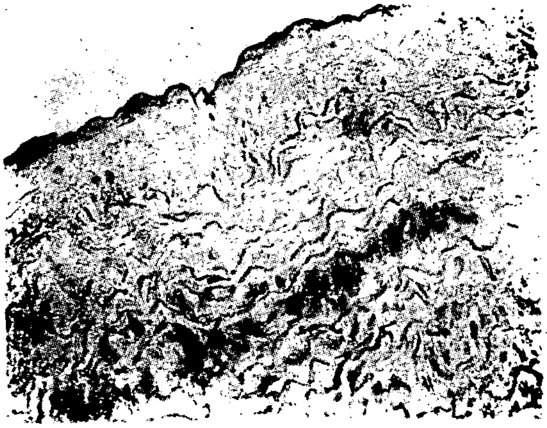

Figure 30. Aorta. Fatty infiltration of intercellular substance in middle coat. Magnification 2 × 40, Sudan III.

Figure 31. Aorta. Mucoid swelling in middle coat. Magnification 2 × 40, hematoxylin + eosin.

aorta. Deposition of fatty formations in the intercellular substance of the middle coat and mucoid swelling were noted in others (Fig. 30).

Thus, while no pronounced atheromatose changes were observed in either group of animals ("mountain" and "lowland"), there were /102 lipid deposits in all of the dogs. The muscle fibers in the middle coat of the aorta had been pushed apart to a significant degree by mucoid matter, and they had atrophied locally. Morphological changes of the same type were observed in the aorta

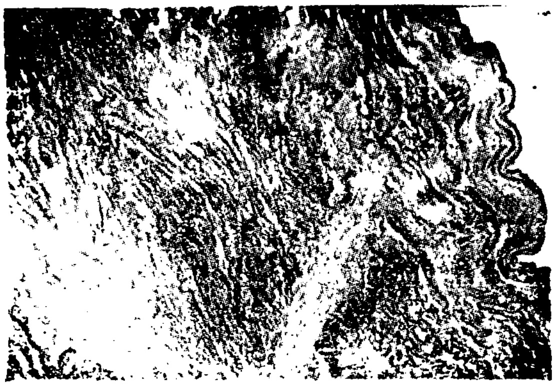

Figure 32. Aorta. Massive scars in middle coat and thickening of intima. Magnification 2 × 40, fuchsilin.

Figure 33. Aorta. Scattered small scars in middle coat. Magnification 2 × 40, hematoxylin + eosin.

Figure 34. Aorta. Massive scars at ramification. Magnification 2 × 20, fuchsilin.

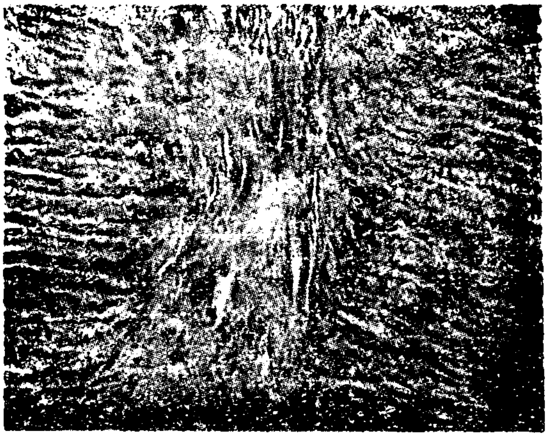

Figure 35. Aorta. cicatricial changes. Magnification 2 × 20, fuchsilin.

wall in the hypertonic animals (both "lowland" and "mountain") that had been treated only with 6-methylthiouracyl: the collagenous and elastic fibers were disintegrating, and the muscle fibers had been /103 pushed apart (Fig. 31) by a strongly basophilic mucoid substance. In some cases, the edema involved only the subintimal zone of the middle coat, while in others it extended throughout the entire thickness of that coat.

There were massive cicatricial changes in the middle coat of the aorta (Figs. 32 and 33) and also at the branching points of the vessels (Fig. 34) in the "urban" dogs. Such changes were /104

Figure 36. Aorta. Small scars in middle coat. Magnification 2 × 40, hematoxylin + eosin.

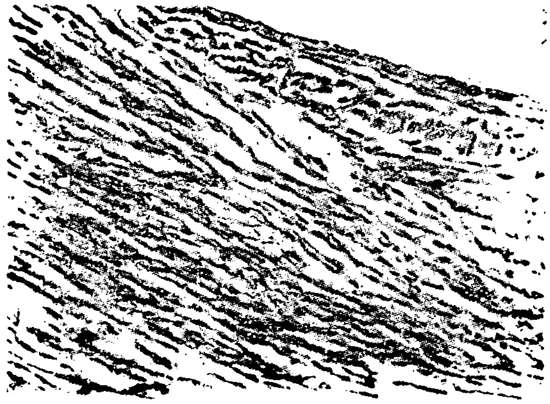

Figure 37. Aorta. Mucoid swelling in middle coat. Magnification 2 × 20, van Gieson's stain.

observed along the course of the vasa vasorum (Fig. 35). Insignificant scarring of the middle coat was also found in the "mountain" dogs (Fig. 36).

Thus, we were unable to find any consistent morphogenetic differences between the "mountain" and "urban" dogs with hypertonia under the 6-methylthiouracyl regime. However, the cicatricial changes were more distinct in the "mountain" dogs. Compared with the "urban" animals that received cholesterol and 6-methylthiouracyl, the edema in the aorta walls of the animals of this series was less severe. /105

It is also necessary to note that there were no lipid deposits at all.

In the animals with "pure" hypertonia, the changes in the aorta wall were less distinct, and the intima was only moderately thickened (Fig. 37).

More striking changes in the wall were observed in the animals with hypertonia + hypothyroidism + cholesteremia. Lipids were deposited on the inner coat, something that was not observed in the animals with "pure" hypertonia, nor even in the animals with hypertonia + hypothyroidism.

Thus, the hypercholesteremia, which was more pronounced among the animals with hypertonia + hypothyroidism + exogenous cholesterol, found its morphological expression in more rapid modification of the aorta wall.

CONCLUSION /106

Modelling of atherosclerosis against a background of prior induced hypertonia, with the consequent inclusion of the hemodynamic, mechanical factor (according to A.L. Myasnikov) into the pathogenetic chain of the disorder (hypertonia + cholesterol-6-methylthiouracyl regime) produced important theoretical results not only under ordinary conditions, but also in the mountain environment.

Concerning the hypertonia itself, its course is benign under the conditions of the mountain climate (2150 m), and a decrease in the arterial-pressure level was observed during the summer. Admittedly, the uncomfortable weather conditions of the fall and winter cause relapses into this "disease." In the animals with hypertonia and thyroid hypofunction compounded by hypercholesteremia, the course of the hypertonia during the first few months of the stay in the mountains was of benign nature, but later, under the cholesterol + 6-methylthiouracyl regime and the deteriorating weather, arterial pressures increased. However, the hypertonia still took a more favorable course in the mountains than on the "lowlands."

Dogs of all groups showed higher blood cholesterol levels under mountain than under "lowland" conditions. In the animals with "pure" hypertonia, cholesterol content varied in the initial range, but when it was combined with thyroid hypofunction there was a tendency to hypercholesteremia; the latter was most pronounced in hypertonia with the cholesterol-6-methylthiouracyl regime.

The amount of lecithin varied in parallel with the cholesterol-level variations; in the dogs with "pure" hypertonia that were subjected to the cholesterol-methylthiouracyl regime in the mountains (last three months), the lecithin levels showed a sharp rise, with the result that the lecithin-cholesterol ratio also increased. This effect can be regarded as helpful (in the sense of preventing lipidosis of the vessels) and linked with the observed absence of typical morphological changes, i.e., athero- /107
matosis in the aorta. To a certain degree, adaptation of the organism to the mountain climate inhibits the development of the atherosclerotic process. In the main, the characteristic lesions in the aorta were observed only in two hypertonic dogs.

A.L. Myasnikov was correct in concluding that hypertonia can sometimes inhibit the development of atherosclerosis. Recently, one of his students - I.K. Shkhvatsabaya (1969) - also voiced support for this view: "We induced various forms of the combination of hypertonia with atherosclerosis in animal experiments.

The laboratory data not only confirmed the clinical observations, but also permit us to advance the following hypothesis: to a definite degree, the outcome of atherosclerosis in hypertonia is determined by the permeability of the vessels." He attaches great importance to the development of collaterals – "supplementary vessels that supply the heart with blood."

As we noted above, our investigation was made on dogs with hypertonia, i.e., the atherosclerosis was superimposed on previously induced hypertonia. If our results are compared with those of M.Ya. Shchukina (1967), it is seen that atherosclerotic damage to the aorta and other organs is encountered much more frequently in the normotonic than in the hypertonic animals. And this effect is observed under both "lowland" and alpine conditions. For example, of 15 previously intact dogs that were subjected to the cholesterol-methylthiouracyl regime at Frunze for nine months, macroscopic changes of one degree or another were observed in the aortas of 10 (lipid maculae in five, plaques in four, and ulcerated plaques in one).

According to our data, only two of the ten dogs with hypertonia suffered changes in the aorta at Frunze after nine months of treatment with cholesterol and methylthiouracyl. Consequently, by itself, the hypertonia had an inhibiting effect on the development of atherosclerosis.

Obviously, subtle biochemical mechanisms that are still unknown to us are at the bottom of this effect. At the same time, we cannot negate the importance of the collaterals of the heart in view of the previously induced hypertonia.

"The heart has really tremendous reserves of resistance to unfavorable external and internal disturbances," writes I.K. Shkhvatsabaya. "It is known, for example, that as constricted arteries reduce its blood supply, larger numbers of supplementary collateral vessels develop in the myocardium. It is these vessels /108
that offset the deficiencies of oxygen and other substances involved in energy metabolism." The hypertonia that preceded and accompanied (for about a year) the induction of atherosclerosis did not accelerate its development but, to the contrary, prevented it. It can be assumed that the arteriolar spasm that is typical in hypertonia "adapts" the heart to an artificially imposed oxygen deficiency. Thus its "reserves of resistance" were fully preserved during the modelling of atherosclerosis.

The results of observations made under high-mountain conditions have their own distinctive features. This is because the adaptation of the organism to relative oxygen deficiency in the mountains increases its general nonspecific resistance (N.N. Sirotinin, V.V. Parin, Z.I. Barbashova, M.M. Mirrakhimov, M.A. Aliyev, N.A. Agadzhanyan, and others). A number of studies made in the high mountains have shown that adaptation of the organism to hypoxemia prevents hypertonia (M.A. Aliyev, S.I. Arestova), myocardial infarct (K.M. Pogodina, T.P. Pal'chun, G.A. Zakharov), experimental epilepsy (T.I. Ivakova), fibrillation of the heart (K.A. Azhibayev and I.K. Mishchenko), etc.

The beneficial influence of the mountain climate was also manifested in regard to atherosclerosis.

M.Ya. Shchukina's studies on intact dogs showed that a three-month stay in the mountains during modelling of atherosclerosis (cholesterol-methylthiouracyl regime) slowed down the emergence of the "atherosclerotic disease." The aortal plaques were resorbed in seven of thirteen "mountain" dogs as compared with 10 of 15 "urban" animals, and in no case did they ulcerate. In our experiments (Chapter V), plaques were found in the aortas of only two out of ten hypertonic dogs. All of the other changes in the vessel walls were typical for hypertonia, which preceded (by 3-6 months) modelling of atherosclerosis.

"Our country has mountainous regions in which there is not enough oxygen in the atmospheric air. It may be assumed," writes I.K. Shkhvatsabaya, "that the deficient supply to the heart muscle is also compensated in these areas by the development of a heavy network of collaterals."

On the basis of many years' experience, the pathological anatomist B.F. Malyshev concluded that lifelong inhabitants of the high mountains seldom suffer from atherosclerosis or myocardial infarct. The beneficial and sanigenic influence of the mountain climate on hypertonia has already been demonstrated experimentally and by clinical statistics (M.A. Aliyev); the incidence of hypertonia among native inhabitants of the mountains is comparatively low (M.M. Mirrakhimov). The expeditionary work of A.V. Zubenko of our laboratory produced interesting results on lipid metabolism in natives of the high mountains (Sary-Tash, Alay, 3200 m). /109

The diet of inhabitants of the mountainous Alay Valley region consists for the most part of meat with a high content of animal fats. We should therefore expect a high cholesterol level. However, the average cholesterol level in the blood of the subjects examined was 164±2.9 mg-% with variations from 112 to 252 mg-%, or substantially lower than it is on the lowlands (212-252 mg-%).

According to A.L. Myasnikov, the lipoprotein figures for healthy individuals vary from 66 to 74% (averaging 70%). An increase in these substances in the blood of atherosclerotics is observed not only with a high blood cholesterol level, but in some cases together with a normal cholesterol content. As a criterion, this phenomenon is more characteristic as compared not only with hypercholesteremia but also with a lowered phospholipid:cholesterol ratio.

Lipoprotein contents were determined in 93 lifelong inhabitants of the high mountains. The average level among the subjects (irrespective of sex) was 71%, with variations from 52 to 80%, while the average lipoprotein content in the foothills reached 29%, with variations from 20 to 48%.

Thus, lifelong inhabitants of the high mountains have normal lipoprotein levels, and the failure of these levels to increase with age can be regarded as an advantageous displacement in the metabolic processes.

The phosphorus-containing lipids of the blood — the phospholipids — bear a definite relation to cholesterol. The normal lecithin level in the blood varies quite widely, from 130 to 240 mg-%. In the healthy human, the lecithin-cholesterol ratio undergoes no substantial change over a rather long period, although it cannot be referred to as constant (A.L. Myasnikov). Instead, this indicator tends to reflect the "readiness" or "stability" of the cholesterol with respect to infiltration of the vessel walls.

The average blood serum phospholipid level of the inhabitants of the Alay was 187±5.3 for men and 190±6.0 for women, with extremes of 107 and 312 mg-%. The lecithin-cholesterol ratios were /110
1.15±0.03 for men and 1.20±0.03 for women.

Phospholipid level tends to increase with age; it is somewhat higher among women than among men. The phospholipid/cholesterol ratio changes little with age; nor are there any substantial differences in these indicators between men and women.

Thus, the lifelong inhabitants of the mountains were found to have low blood serum cholesterol levels together with normal phospholipid and lipoprotein contents; their phospholipid:cholesterol ratios were at the normal level. These data indicate the absence of any disturbances in lipoid metabolism, especially among the older age groups.

Our experimental data indicating a marked degree of stability against atherosclerosis under the conditions of the mountain climate are confirmed by the results of clinical biochemical studies. The fact that the mountain climate has a favorable influence on atherosclerosis has been established, but the subtle mechanism of this phenomenon must be the object of further study. New data have already been obtained in this context at our laboratory (1969 and 1970): the mountain climate (elevation 2150 meters, Okchorkoy) "heals" hypertonia during the summer, activates the anticoagulant system, and increases the amount of heparin in it (Sh. Dyushenaliyeva), and this, in our opinion, explains the absence of complications (thrombosis, infarct, fatal outcome). "Aborigines," i.e., dogs that are born and raised in the mountains, show resistance to hypertonia (A. Azibaliyev) and infarct (T. Pal'chun).

According to the results obtained by Graduate Student K. Isayev on hypertonia (more than 150) and atherosclerosis (more than 100) patients, a 26-day vacation under middle-mountain conditions (1610 m, "Goluboy Issyk-Kul'") definitely lowers their arterial pressure and cholesterol levels but increases the lecithin levels and lecithin-cholesterol ratios. These shifts are highly important from the prognostic standpoint and echo our experimental data, which indicate a favorable effect of mountain adaptation in hypertonia and atherosclerosis.

REFERENCES

/111

1. Abdullayev, D.M. Azerb. med. zhurnal, 1955, 3, 53.
2. Abdullayev, R.A. Kardiologiya, 1962, 3, 54.
3. Abol'yanina, Ye. I. Tr. Astrakhansk. med. in-ta, II, 1954, 275.
4. Avakyan, V.M. Tr. Yerevansk. med. in-ta, 10, 1959, 267.
5. Aleksandrova, A.F. and Yegorov, P.I. Tr. Voyenno-med. Akad. RKKA im. S.M. Kirova, 16, 1938, 249.
6. Aliyev, M.A. Izv. Akad. Nauk Kirgiz. SSR, 3, 1956, 127.
7. Aliyev, M.A. In book: Materialy I Kavkazsk. med. resp. konf. po voprosam patologich. fiziologii (Materials of the First Caucasus Medical Republican Conference on Problems of Pathophysiology), Baku, 1958, 34.
8. Aliyev, M.I. and Volkova, V.A. Tr. In-ta krayevoy meditsiny Akad. Nauk Kirgiz. SSR, Frunze, 2, 1959, 13.
9. Aliyev, M.A. Tr. In-ta krayevoy meditsiny Akad. Nauk Kirgiz. SSR, Frunze, 2, 1959, 5.
10. Aliyev, M.A. In book: Problemy kompensatsii, eksperimental'noy terapii i luchevoy bolezni (Problems of Compensation, Experimental Therapy, and Radiation Sickness), Moscow, 1960, 248.
11. Aliyev, M.A. Tr. konf. po vysokogor'yu i kholodovoy travme (Transactions of Conference on the High Mountains and Cold Trauma), Frunze, 1962, 95.
12. Aliyev, M.A. Author's abstract of Doctorate Thesis, Moscow, 1964.
13. Aliyev, M.A. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological)" and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 43.
14. Aliyev, M.A. and Arestova, S.I. Materialy III godichnoy nauchnoy sessii In-ta krayevoy meditsiny (Materials of Third Annual Scientific Session of the Institute of Regional Medicine), Frunze, 1966, 34.
15. Allaberdyyev, A.A. Vopr. klimatopatologii v klinike serdechno-sosudistykh zabolevaniy (Problems of Climatopathology in the Clinical Medicine of Cardiovascular Diseases), Moscow, 1961, 206.
16. Amatunyan, V.G. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological)" and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 50.

17. Anichkov, N.N. and Khalatov, S.S. Tr. o-va russkikh vrachey v S.-Peterburge (Transactions of the Society of Russian Physicians at St. Petersburg), 1912-1913, 90.
18. Anichkov, N.N. Arkhiv biologicheskikh nauk, 1925, 2, 5, 246.
19. Anichkov, N.N. Sovetskiy vrach, 1937, 21, 1605.
20. Anichkov, N.N. and Tsinzerling, V.D. In book: Ateroskleroz (Atherosclerosis), Akad. Med. Nauk SSSR, 1953, 7.
21. Anichkov, N.N. and Volkova, K.G. Tezisy dokladov nauchnoy sessii, posvyashchennoy problemami fiziologii i patologii serdechno-sosudistoy sistemy v Leningrade (Abstracts of Papers at Scientific Session on Problems of Physiology and Pathology of the Cardiovascular System at Leningrad), Tbilisi, 1955, 45.
22. Antonenko, V.T. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya" (v norme i patologii) i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological): and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 52.
23. Atabekov, Yu.A. Tezisy dokladov nauchnoy konferentsii po problemam fiziologii i patologii serdechno-sosudistoy sistemy (Abstracts of Papers at Scientific Conference on Problems of the Physiology and Pathology of the Cardiovascular System), Tashkent, 1963, 3.
24. Afonskiy, N.P. Klinicheskiye lektsii po vnutrennim boleznyam (Clinical Lectures on Internal Diseases), Baku, 1953.
25. Akhunbayev, I.K. Sb. trudov IV Kirgiz. gos. med. in-ta (Collected Transactions of the Fourth Kirgiz State Medical Institute), 1949, Frunze, 94. /112
26. Akhundov, D.K. Klinich. med., 1959, 7, 59.
27. Ashof, L. Tr. I. Mosk. med. in-ta, 1935, 3.
28. Bavina, M.V. Author's abstract of Candidate's Thesis, Moscow, 1951.
29. Bedalova, S.M. and Effendiyev, M.E. Azerb. med. zhurnal, 1958, 3, 74.
30. Brodovich, L.A. In book: Gipertonicheskaya bolezn' (Hypertonia), Leningrad, 1946, 52.
31. Burmin, L.S. Sovetskoye zdravookhraneniye Kirgizii, 1963, 3.
32. Vanga and Khu, 1957, Cited from A.L. Myasnikov, 1965.
33. Vanshteyn, Kh.I. Vrachebnoye delo, 1929, 13-14, 841.
34. Vasilenko, M.Ye. In collection: Funktsii organizma v usloviyakh izmenennoy gazovoy sredy (The Functions of the Organism under the Conditions of a Modified Gaseous Environment), Moscow-Leningrad, 1955, 161.
35. Veselkin, N.V. Russkiy vrach, 1912, 39, 1951.
36. Vlasova, V.A. Tezisy dokladov nauchno-prakticheskoy konferentsii, posvyashchennoy voprosam lecheniya bol'nykh s zabolevaniyem serdtsa (Abstracts of Papers at Scientific-Practical Conference Devoted to the Problems of Treating Patients with Heart Disease), Pyatigorsk, 1960, 62.

37. Volkova, K.G. Tr. Leningr. fil. Vsesoyuz. in-ta eksperim. medits. (Transactions of Leningrad Branch of the All-Union Institute of Experimental Medicine), Leningrad, Medgiz, 1946.
38. Volkova, K.G. In book: Ateroskleroz (Atherosclerosis), Moscow, 1953, 53.
39. Volkova, K.G. Tr. XIV Vsesoyuz. s"yezda terapevtov (Transactions of Fourteenth All-Union Conference of Therapists), Moscow, 1958, 45.
40. Gevondyan, Ye.S. Farmakologiya i toksikologiya, 1950, 2, 3.
41. Gel'man, I.G. Essentsial'naya gipertoniya (Essential Hypertonia), Moscow, 1927.
42. Georgiyevskiy, K.N. Dissertation, St. Petersburg, 1896.
43. Glazunov, I.S. Kardiologiya, 1961, 3, 30.
44. Glushchenko, A.G. Sb. tr. respubl. sudebno-med. ekspertizy i kafedry sudebnoy meditsiny. Dushanbinsk. med. in-ta (Collected Transactions of the Republic Forensic Medicine Expert Council and the Department of Forensic Medicine at the Dushanbe Medical Institute), Dushanbe, 1950, 1, 39.
45. Gol'tskener, S.L. Itogovaya nauchnaya konferentsiya za 1949 g. Novosibirsk. med. in-ta (Review Scientific Conference of the Novosibirsk Medical Institute for 1949), Novosibirsk, 1950, 43.
46. Goncharova, L.S. Arkhiv patologii, 1957, 12, 29.
47. Gornak, K.A. Tr. simpoziuma po aterosklerozu (Transactions of a Symposium on Atherosclerosis), Kuybyshev, 1959.
48. Grinshteyn, B.Ya. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological) and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 56.
49. Grobovinskiy, Ye.B. Tr. Akad. med. nauk SSSR, 20, 2, 1952, 144.
50. Gruzin, A.I. Gipertonicheskaya bolezn' (Hypertonia), Kiev, 1952.
51. Gukasyan, G.M. Sovetskaya meditsina, 1964, 3, 25.
52. Daraseliya, I.N. Doklad na I soveshchaniye po epidemiologii gipertonicheskoy bolezni i koronarnogo ateroskleroza (Paper at First Conference on the Epidemiology of Hypertonia and Coronary Atherosclerosis), Moscow, 1962, 37.
53. Dvizhkov, P.P. Novosti med. izd. Akad. med. nauk SSSR, 1948, 7, 37.
54. Dzhaylobayev, A.D., Isakova, S.I., Mirrakhimov, M.M., and Tilis, A.Yu. Meterialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological)" and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 63.
55. Don-Dog. 1958. Cited from A.L. Myasnikov, 1965.

56. Drobova, G.V. Tr. Leningr. oblastnogo gospitalya dlya lecheniya invalidov Otechestvennoy voyny (Transactions of the Leningrad Regional Hospital for Treatment of Second World War Invalids), Leningrad, 1948, 325.
57. Zhidovtseva, M.I. Tezisy dokladov nauchnoy sessii khar'kovsk. med. stomatologicheskogo in-ta (Abstracts of Papers at Scientific Session of the Khar'kov Medical Stomatological Institute), 1959, 16.
58. Zhukov, A.P. In book: Problemy sovetskoy fiziologii, biokhimii i farmakologii (Problems of Soviet Physiology, Biochemistry, and Pharmachology), Moscow, 1949, 63.
59. Zhukova, A.A. Terapevticheskiy arkhiv, 1963, 35, 70.
60. Yegorova, L.I. Candidate's Thesis, Moscow, 1950.
61. Ignatovskiy, A.I. and Saltykov, S.N. Izv. Voyenno-med. akad. /113
1908, 16, 2, 154.
62. Il'inskiy, B.V. In book: VNEM. Stenogramma konf. po aterosklerozu (All-Union Scientific Research Institute of Experimental Medicine. Transcript of Conference on Atherosclerosis), 5, VI, 1938, 1, 5.
63. Il'inskiy, B.V. Klinicheskaya meditsina, 1940, 18, 1, 55.
64. Il'inskiy, B.V. Terapevticheskiy arkhiv, 1951, 23, 5, 39.
65. Il'inskiy, B.V. Materialy k etiologii, patogenezu i klinike ateroskleroza (Materials on the Etiology, Pathogenesis, and Clinical Treatment of Atherosclerosis), Doctorate Thesis, 1954.
66. Il'inskiy, B.V. Ateroskleroz (Atherosclerosis), Leningrad, Medgiz, 1960.
67. Ishmukhametova, G.Z. Tezisy dokladov Kazan. med. in-ta, lechebnogo f-ta (Abstracts of Papers of the Kazan' Medical Institute, Therapeutics Department), Kazan', 1956, 13.
68. Kalamkarov, I.G. Dissertation, St. Petersburg, 1907.
69. Kalnyn' E. Sb. nauchnykh rabot Rizhskogo med. in-ta (Collected Scientific Papers of the Riga Medical Institute), Riga, 1954, 229.
70. Kasimov, G.I., Guseynov, G.A., and Guseyn-Zade, G.A. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy ogranizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological)" and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 65.
71. Kipshidze, N.N. Influence of Oxygen Starvation on the Development of Experimental Atherosclerosis of the Coronary Arteries, Byull. biologii i meditsiny, 1959, 47, 4, 54.
72. Kipshidze, N.N., Chumburidze, I.T., Chapidze, G.E., and Katamadze, N.I. Tezisy dokladov soveshchaniya po epidemiologii gipertonicheskoy bolezii i koronarnogo ateroskleroza (Abstracts of Papers at a Conference on the Epidemiology of Hypertonia and Coronary Atherosclerosis), 1965, 72.
73. Kleonina, A.A. In book: Ateroskleroz i koronarnaya nedostatochnost' (Atherosclerosis and Coronary Insufficiency), Moscow, Medgiz, 1956, 209.

2

74. Kogan-Yasnyy, V.M. Osnovy i dostizheniya sovetskoy meditsiny, 1938, 4, 170.
75. Konoval'chik, N.I. In book: Voprosy kardiologii i gematologii (Problems of Cardiology and Hematology), 1940, 89.
76. Kochekmadze, S. Tezisy dokladov II nauchn. konf., posvyashchennoy 85-letiyu so dnya rozhdeniya V.I. Lenina (Abstracts of Papers at Second Scientific Conference Dedicated to the 85th Anniversary of V.I. Lenin's Birth), Tbilisi, Izd. Tbilissk. gos. med. in-ta, 1955, 48.
77. Kochum'yan, A.A. In book: Kislorodnaya nedostatochnost' (Oxygen Insufficiency), Kiev, 1963, 485.
78. Kritsman, M.G. and Bavina, M.V. In book: Ateroskleroz i koronarnaya nedostatochnost' (Atherosclerosis and Coronary Insufficiency), Moscow, 1956, 126.
79. Krylov, D.D. Izv. VMA, 1916, 32, 3, 323.
80. Kurmanovskaya, I.M., Chernyakov, S.N., Ivanova, Ye.A., and Yemel'yanova, I.R. Sovetskaya meditsina, 1952, 8, 29.
81. Kuchuk, E.M. Vliyaniye vysokogornogo klimata i ingibitora monoaminoksidazy - iprazida na funktsional'noye sostoyaniye shchitovidnoy zhelezy i pokazateli lipidnogo obmena u zdorovykh krolikov i krolikov s eksperimental'nym aterosklerozom (Influence of the Mountain Climate and the Monoaminooxidase Inhibitor Iprazide on the Functional State of the Thyroid Gland and the Lipid-Metabolism Indicators in Healthy Rabbits and Rabbits with Experimental Atherosclerosis), Author's abstract, Frunze, 1969.
82. Lavrent'yev, L.N. Tezisy dokladov 2-y nauchnoy konferentsii po probleme zhira v pitanii (Abstracts of Papers at Second Scientific Conference on the Problem of Fats in Nutrition), Leningrad, 1962, 291.
83. Lang, G.F. Arkhiv Gosudarstvennogo klinicheskogo instituta usovershenstvovaniya vrachey, 1, 1922, 16.
84. Lang, G.F. Gipertonicheskaya bolezn' (Hypertonia), Leningrad, Medgiz, 1950.
85. Laufer, M.Ya. Kardiologiya, 1962, 3, 64.
86. Levina, Ts.A. Vrachebnoye delo, 1949, 2, 138.
87. Levinson, M.O. Tr. Rostovsk. gos. med. in-ta. Rostov-on-Don, 1940, 136.
88. Levchenko, M.A., Spesivtseva, V.G., and Shishkova, A.M. Terapevticheskiy arkhiv, 1956, 28, 6, 71.
89. Leytes, S.M. In book: Fiziologiya i patofiziologiya zhirovogo /114
obmena (Physiology and Pathophysiology of Fat Metabolism), Kiev, 1937, 5.
90. Lisovskiy, V.A. and Khlybov, G.N. Tezisy dokladov I Vseros. s"yezda terapevtov (Abstracts of Papers at First All-Russian Congress of Therapists), Moscow, 1958, 124.
91. Litvak, F.I. and Sosnina, I.M. Terapevticheskiy arkhiv, 1954, 26, 3, 30.
92. Lifshits, A.V. Fiziologicheskiy zhurnal, 35, 1, 1949, 3.
93. Loginov, A.S. Tr. 1 MOLMI (Transactions of the First Moscow Order of Lenin Medical Institute), Moscow, 1956, 1, 168.

94. Lukomskiy, P.Ye. In book: Sovremenyye problemy kardiologii (Contemporary Problems of Cardiology), 1960, 129.
95. Lyamtsev, V.T. Arkhiv patologii, 1957, 19, 3, 29.
96. Maksimova, I.V. Tr. LSGMN. Serdechno-sosudistaya patologiya (Trans. Leningrad Sanitation and Hygiene Medical Institute, Cardiovascular Pathology), 1958, 40, 72.
97. Magrupov, A.I., Semenov, Ye.N., Azizova, O.M., Petrusheva, T.M., Abdukhalinova, F.A., Rostovtseva, A.A., and Gamiyants, S.A. Voprosy fiziologii i patologii serdechno-sosudistoy sistemy (Problems in the Physiology and Pathology of the Cardiovascular System), Tashkent, 1964, 88.
98. Maksudov, B.S. and Lushnikova, L.A. Tezisy dokladov 14-go Vsesoyuzn. s"yezda terapevtov (Abstracts of Papers at 14th All-Union Conference of Therapists), Moscow, 1956, 25.
99. Mansurov, Kh.Kh. and Kostenko, Z.A. In book: Voprosy klimatopatologii v klinike serdechno-sosudistykh zabolevaniy (Problems of Climatopathology in the Clinical Treatment of Cardiovascular Diseases), Moscow, 1961, 198.
100. Matvishvili, G.I. Tezisy dokladov IV soveshchaniya po epidemiologii gipertonicheskoy bolezni i koronarnogo ateroskleroza (Abstracts of Papers at 4th Conference on the Epidemiology of Hypertonia and Coronary Atherosclerosis), 1965.
101. Mel'nichuk, S.P. In book: Kislorodnaya nedostatochnost' (Oxygen Insufficiency), Kiev, 1963, 479.
102. Mirrakhimov, M.M. Sovetskoye zdravookhraneniye Kirgizii, 1960, 45.
103. Mirrakhimov, M.M., Aytkulova, A.U. and Dneprovskaya, V.S. Tezisy dokladov na II konferentsii po klimatologii serdechno-sosudistoy sistemy (Abstracts of Papers at Second Conference on the Climatology of the Cardiovascular System), Moscow, 1962, 24.
104. Mirrakhimov, M.M. Ocherki o vliyanii gornogo klimata Sredney Azii na organizm (Notes on the Influence of the Mountain Climate of Central Asia on the Organism), Frunze, 1964.
105. Moiseyeva, Z.S. Cited from M.M. Mirrakhimov, 1964.
106. Mokhnacheva, A.I. Farmakologiya i toksikologiya, 1950, 2, 5.
107. Myasnikov, A.L. Terapevticheskiy arkhiv, 1924, 2, 5-6, 411.
108. Myasnikov, A.L. Leningradskiy meditsinskiy zhurnal, 1927, 2, 91.
109. Myasnikov, A.L. Sovetskaya meditsina, 1949, 2, 1.
110. Myasnikov, A.L. Tezisy dokladov na VIII sessii AMN SSSR (Abstracts of Papers at the Eighth Session of the USSR Academy of Medical Sciences), 1953.
111. Myasnikov, A.L. Gipertonicheskaya bolezn' (Hypertonia), Moscow, Medgiz, 1954.
112. Myasnikov, A.L. Klinicheskaya meditsina, 1956, 6, 65.
113. Myasnikov, A.L. Terapevticheskiy arkhiv, 1959, 31, 4, 126.
114. Myasnikov, A.L. Ateroskleroz (Atherosclerosis), Moscow, 1961.
115. Myasnikov, A.L. In book: Gipertonicheskaya bolezn' i ateroskleroz (Hypertonia and Atherosclerosis), Moscow, 1965.

116. Nedzvetskiy, S.V. and Ratnitskaya, S.S. Biokhimiya, 1958, 16, 5, 24.
117. Orlovskiy, Z.F. Russkiy vrach, 1905, 46, 1443.
118. Paranskiy, A.G. Vrachebnoye delo, 1949, 7.
119. Perera, D.A. In book: Sovr. problemy kardiologii (Contemporary Problems of Cardiology), USSR Academy of Medical Sciences Institute of Therapeutics, Moscow, 1960, 189.
120. Petrovskiy, B.V. and Krylov, V.S. Kardiologiya, 6, 1966, 10.
121. Popov, V.G. and Grinshpun, L. D. Vrachebnoye delo, 1951, 10, 883.
122. Pressman, L.P., Kogan, Ts.Ya., and Atlasova, A.L. In collection: Teoriya i praktika klinicheskoy meditsiny (Theory and Practice of Clinical Medicine), 1952, 4, 54.
123. Prikhod'kova, Ye.K. and Kalmykova, K.M. Uchenyye zapiski Ukrainskogo instituta eksperimental'noy endokrinologii /115
(Scientific Annals of the Ukrainian Institute of Experimental Endocrinology), Moscow, 1953, 121.
124. Pushkar', Yu.T. In book: Ateroskleroz (Atherosclerosis), Moscow, 1953, 121.
125. Ratner, N.A. and Spivak, G.L. Terapevticheskiy arkhiv, 1960, 32, 9, 15.
126. Rozhdestvenskiy, Ya.N. Tr. AMN SSSR. Gipertonicheskaya bolezn' (Trans. Acad. Med. Sci. USSR. Hypertonia), 1952, 2, 96.
127. Sergeyev, Yu.V. Voprosy fiziologii i patologii vysokogor'ya (Problems of the Physiology and Pathology of the High Mountains), Dushanbe, 1963, 62, 81.
128. Sinitsina, T.A. In book: Ateroskleroz (Atherosclerosis), 1953, 68.
129. Sinitsina, T.A. Byull. eksp. biol. i med., 1955, 39, 2, 29.
130. Sinitsina, T.A. and Lovyagina, T.N. Dokl. Akad. Nauk SSSR, 1959, 127, 4, 931.
131. Sinitsina, T.A. Meditsina, 1964.
132. Sirotinin, N.N. Voprosy fiziologii i patologii vysokogor'ya (Problems of the Physiology and Pathology of the High Mountains), Dushanbe, 1932, 62.
133. Sirotinin, N.N. In book: Fiziologiya i patologiya dykhaniya. Gipoksiya i oksigenoterapiya (Physiology and Pathology of Respiration. Hypoxia and Oxygen Therapy), Kiev, 1958, 82.
134. Sirotinin, N.N. Materialy simpoziuma "Gazoobmen v usloviyakh vysokogor'ya (v norme i patologii)" i konferentsii "Vysokogornyy klimat i bol'noy organizm" (Materials of Symposium on "Gas Metabolism Under the Conditions of the High Mountains (Normal and Pathological)" and Conference on "The Mountain Climate and the Diseased Organism"), Frunze, 1965, 79.
135. Smolenskiy, V.S. Author's abstract of Candidate's Thesis, Moscow, 1952, 8.
136. Smolenskiy, V.S. In book: Ateroskleroz (Atherosclerosis), Moscow, 1953, 63.
137. Smolenskiy, V.A. Byull. eksp. biol. i med., 1960, 6, 111.
138. Smol'yannikova, A.V. and Naddachina, T.N. Kardiologiya, 1961, 4, 14.

139. Sokolov, N.A. Tr. 8-go s"yezda terapevtov (Transactions of 8th Congress of Therapists), 1925, 37.
140. Starokadomskiy, L.D. and Sobolev, L.V. Dissertation, St. Petersburg, 1909.
141. Strazhesko, N.D. Klinicheskaya meditsina, 1940, 18, 5, 5.
142. Stukkey, N.V. Dissertation, St. Petersburg, 1910.
143. Sya Zhen'-I. In book: Ateroskleroz (Atherosclerosis), Leningrad, 1961, 105.
144. Tareyev, Ye.M. and Ratner, N.A. Trudy terapevticheskoy kliniki I MOLMI (Transactions of the Therapeutics Clinic of the First Moscow Order of Lenin Medical Institute), 1938, 3.
145. Tareyev, Ye.M. Gipertonicheskaya bolezn' (Hypertonia), Moscow, 1948.
146. Tareyev, Ye.M. Vnutrenniye bolezni (Internal Diseases), Moscow, 1952.
147. Tokar', N.I. Sovetskoye zdravookhraneniye Kirgizii, 1959, 6, 35.
148. Tatarskiy, V.V. and Tsinzerling, V.D. Arkhiv patologii, 1950, 1, 44.
149. Terent'yeva, N.A. Klinicheskaya meditsina, 1957, 4.
150. Turkel'taub, M.S. Tr. In-ta klinich. i eksp. kardiologii, 8, 1949, 14.
151. Turmambetov, S. Author's abstract of Thesis, Frunze, 1960.
152. Ul'yanova, S.A. and Shumitskaya, N.M. In book: Kislorodnaya nedostatochnost' (Oxygen Insufficiency), Kiev, 1963, 491.
153. Umidova, Z.I., Aristova, Z.V., and Niyazova, Kh. In book: Voprosy klimatopatologii v klinike serdechno-sosudistykh zabolevaniy (Problems of the Climatology and Clinical Medicine of Cardiovascular Diseases), Moscow, 1961, 173.
154. Umidova, Z.I., Inoyatova, L.Kh., and Lazarenko, L.I., Med. zhurnal Uzbekistana, 1962, 18, 3.
155. Urbanyuk, K.G. Vrachebnoye delo, 1959, 1, 93.
156. Filatova, L.G. Issledovaniya po fiziologii vysotnoy akklimatizatsii zhivotnykh i cheloveka (Research on the Physiology of Altitude Acclimatization of Animals and Man), Frunze, 1961.
157. Khalatov, S.S. Dissertation, Petrograd, 1917.
158. Kharlamovich, S.I. Tr. Turkm. gos. med. in-ta, 1960, 10, 73.
159. Tsinzerling, V.D. Arkhiv biologicheskikh nauk, 1926, 26, 1-3, 141.
160. Tsukershteyn, Ye.I. and Yegorova, M.N. Vrachebnoye delo, 1949, 3, 64.
161. Chernysh, P.A. Voprosy kurortnogo dela v Uzbekistane (Problems of Health-Resort Administration in Uzbekistan), Collection 12, Tashkent, 1951, 173. /116
162. Shagalova, K.A. and Estrin, P.L. Sb. trudov Tashkent. med. in-ta usovershenstvovaniya vrachey (Collected Transactions of the Tashkent Medical Institute for the Advancement of Physicians), 1952, 142.
163. Shakhnazarov, A.B. Klinicheskaya meditsina, 1953, 10, 25.

164. Shershevskiy, G.M. In collection: Nekotoryye problemy vnutrenney meditsiny (Certain Problems of Internal Medicine), Novosibirsk, 1936, 102.
165. Shershevskiy, G.M. Referaty i tezisy dokl. Stalinskogo in-ta usovershenstvovaniya vrachey (Summaries and Abstracts of Papers of the Stalino Institute for the Advancement of Physicians), 1956, 27.
166. Shurygin, A.Ya. Tr. konf. po vysokogor'yu i kholodovoy travme (Transactions of Conference on the High Mountains and Cold Trauma), Frunze, 1962, 42.
167. Shukina, M.Ya. Tezisy dokladov I godichnoy nauchnoy sessii In-ta krayevoy meditsiny AMN SSSR (Abstracts of Papers at the First Annual Scientific Session of the Institute of Regional Medicine, USSR Academy of Medical Sciences), Frunze, 1964, 32.
168. Shchukina, M.Ya. Materialy II godichnoy nauchnoy sessii AMN SSSR i AN Kirgiz SSR (Materials of Second Annual Scientific Session of the USSR Academy of Medical Sciences and the Kirgiz Academy of Sciences), Frunze, Institute of Regional Medicine, 1965, 53.
169. Shchukina, M.Ya. and Zubenko, A.V. Materialy III godichnoy (vyyezdnoy) sessii AN Kirgiz. SSR i AMN SSSR (Materials of Third Annual (Excursion) Session of the Kirgiz Academy of Sciences and the USSR Academy of Medical Sciences), Frunze, Institute of Regional Medicine, 1966.
170. Yushchenko, N.A. Byull eksp. biol., 1959, 3, 31.
171. Yakovleva, A.P. and Shvarts, L.S. Terapevticheskiy arkhiv, 1929, 7, 4, 406.
172. Yastrebtsova, N.L., Gornak, K.A., Kondzhuntseva, E.A., Makarova, N.A., and Shmul'yan, T.R. In book: Ateroskleroz (Atherosclerosis), Moscow, 1961, 117.
173. Ahrens, E.H. and Kunkel, H.G. J. Clin. Invest., 1949, 28, 6, 1544-1565.
174. Altland, Paul D. Arch. Pathol., 1960, 70, 3, 349-357.
175. Altshul, R. and German, G.H. Arch. Biochem. Biophys., 1954, 51, 1, 308.
176. Altschul, R.Z. Kreislaufforsch., 1955, 44, 3-4, 129.
177. Barr, D., Russ, E., and Eder, H.A. Amer. J. Med., 1951, 11, 480-493.
178. Bevans, M., Davidson, J., and Kendall, F. Arch. Pathol., 1951, 51, 288.
179. Borgstrom, S. and Malmors, H.Z. Krebsforsch., 1960, 49, 201.
180. Boyd, E.M. Trans. Roy. Soc. Can., 1937, 31, 11-16.
181. Bragdon, J. Proc. Soc. Exper. Biol. Med., 1957, 95, 282.
182. Bragdon, J. Circulation, 1952, 5, 641.
183. Brunner, D. and Lobl, K. Ann. Intern. Med., 1958, 49, 4, 732.
184. Buck, R.G. and Rossister, R.J. Arch. Path., 1951, 51, 2, 224-237.
185. Dewey, K. Arch. Intern. Med., 1916, 17, 4, 757-785.
186. Donnison, C.D. Lancet, 1929, 216, 1, 6-7.
187. Ellis. A. Lancet, 1938, 30, 977-980.
188. Fenn, W.O. Physiol. Rev., 1940, 20, 377-415.

189. Fischberg, A.M. Hypertension and Nephritis, Philadelphia, 1954.
190. Gauston, 1965. Cited from A.A. Myasnikov, 1965.
191. Gertler, M.M., Garn, S.M., and Lerman, A.S. Circulation, 1950, 2, 205.
192. Gertler, M.M. and Garn, S.M. Science, 1950, 112, 289, 14-16.
193. Glawson, Bell, 1941. Cited from A.A. Myasnikov, 1965.
194. Gonsales, E. et al., Circulation, 1956, 14, 491.
195. Harris, I., Vernon, C.E., Jacob, H., and Robberts, M.E. Lancet, 1949, 257, 6572, 283-285.
196. Hartfort, W.A. et al., Proc. Soc. Exper. Biol. Med., 1952, 84, 384.
197. Horlick, L. and Katz, L. Amer. Heart J., 1949, 38, 336.
198. Juschar, 1889. Cited from A.A. Myasnikov, 1965.
199. Katz, S.N. and Stamler, J. Experimental Atherosclerosis, Springfield, 1953.
200. Keith, N.M., Wagener, H.P., and Kernohan, I.W. Arch. In- /117
tern. Med., 1928, 41, 141-188.
201. Kellner, A., Correl, J.M., and Ladd, A.T. Amer. Heart J., 1949, 38, 3, 460.
202. Kellner, A., Correl, J.M., and Ladd, A.T. Exper. Med., 1951, 93, 4, 385-398.
203. Kellner, A. Bull. New York Acad. Med., 1952, 28, 1, 11-27.
204. Keys, A., Fidanza, and Scardi, V. Lancet, 1952, 2, 209.
205. Keys, A. and Keys, M.M., Brit. J. Nutr., 1954, 8, 2, 138.
206. Keys, A. JAMA, 1957, 164, 1912.
207. Keys, A. et al., Lancet, 1958, 11, 175.
208. Lindsay, S., Chaikoff, I., and Gilmor, A. Circulation, 1952, 6, 466.
209. Maclachman, P.L. J. Biol., Chem., 1939, 129, 2, 465-469.
210. Mann, G.V. Amer. J. Med., 1957, 23, 3, 463.
211. Malmors, H. Acta Med. Scand., 1950, Suppl. 246, 137.
212. Mallinow, M., Hojman, D. and Pellegrino, A. Acta Cardiol., 1954, 9, 480.
213. Mallinow, M., Hojman, D. and Pellegrino, A. Arch. Pathol., 1956, 61, 11.
214. Masatelli, L. Nature, 1958, 4613, 181.
215. Morrison, L.M. J. Clin. Med., 1952, 39, 4, 550-555.
216. Moss, L. and Dury, A.I. Mount Siani Hosp., 1957, 24, 1047.
217. Padmavati, S. et al., Indian. J. Med. Res., 1958, 46, 2, 245.
218. Page, I.H., Kirk, E. and Van Slyke, D.D. J. Clin. Invest., 1936, 15, 109-113.
219. Page, I. and Brown, H. Circulation, 1952, 6, 681.
220. Peters, I.P. and Man, E.B. J. Clin. Invest., 1943, 22, 5, 707-714.
221. Peters, I.P. and Van Slyke, D.D. Quantitative Clinical Chemistry, Baltimore, 1946.
222. Puddu, V. In: World Trends, Cardiol., 1956, 1, 77.
223. Rau, H. Klin. Wschr., 1956, 167.
224. Ribbert, A. Verhandl. Deutsch. Pathol., 1904.
225. Schemensky, 1937. Cited From van Leer. Anoksiya i yeye vliyaniye na organizm (Anoxia and Its Influence on the Organism), Moscow, 1947.

226. Schwartz, Colin I., Day, et al., Aust. J. Exp. Biol. Med. Sci., 1957, 35, 5, 444-459.
227. Smith, Elspeth B. Lancet, 1957, 2, 7002, 910-914.
228. Steiner, A., Kendal, F.E., and Bevans, M. Amer. Heart. J., 1949, 35, 34.
229. Steiner, A. and Kendal, F.E. Arch. Path., 1946, 42, 433-445.
230. Sydenstricker, D. 1933. Cited from A.A. Myasnikov, 1965.
231. Tung, C.L. et al., J. Clin. Med., 1958, 77, 6, 596.
232. Veil, W., Sturm. Die Pathologie des Stammvirus und ihre vegetativen klinischen Bilder (The Pathology of the Primary Virus and Its Vegetative Clinical Picture), 1939.
233. Waris, A. Acta. Med. Scand., 1958, 161, 337, 7-79.
234. Wakerlin, E. Ann. Intern. Med., 1952, 37, 313.
235. Westphal, K.Z. Ges. Inn. Med., 1924, 230-232.
236. White, P.D. In: World Trends, Cardiol., 1959, 62.
237. Wilgram, G. Circulation, 1957, 163, 500.
238. Volhard, F. and Fahrt. Die breitische Nierenkrankheit (Bright's Disease), 1, Berlin, 1914.
239. Zarcovic, G. et al., Acta. Med. Jugosl., 1955.
240. Zilversmit, D.B., Shore, M.L., and Ackerman, R.F. Circulation, 1954, 9, 4, 581-585.

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